

# HIV Molecular Immunology 2008

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# Contents

<b>Contents</b>	<b>iii</b>		
<b>Preface</b>	<b>v</b>		
Scope and purpose of the HIV molecular immunology database . . . . .	v	II-B-4	Gag p24-p2p7p1p6 CTL/CD8+ epitopes . . . . . 303
About the data . . . . .	v	II-B-5	Gag p2p7p1p6 CTL/CD8+ epitopes . . . . . 306
Citing the database . . . . .	v	II-B-6	Gag CTL/CD8+ epitopes . . . . . 321
About the PDF . . . . .	vi	II-B-7	Gag/Pol CTL/CD8+ epitopes . . . . . 334
Genome maps . . . . .	viii	II-B-8	Gag/Pol TF CTL/CD8+ epitopes . . . . . 334
HIV/SIV proteins . . . . .	ix	II-B-9	Gag/Pol TF-Protease CTL/CD8+ epitopes . . . . . 335
Abbreviations . . . . .	x	II-B-10	Protease CTL/CD8+ epitopes . . . . . 335
Amino Acid Codes . . . . .	xi	II-B-11	Protease-RT CTL/CD8+ epitopes . . . . . 352
		II-B-12	RT CTL/CD8+ epitopes . . . . . 353
<b>Part I. Review Articles</b>	<b>1</b>	II-B-13	RT-Integrase CTL/CD8+ epitopes . . . . . 474
		II-B-14	Integrase CTL/CD8+ epitopes . . . . . 474
<b>I-A Identification and Optimal Definition of HIV-Derived Cytotoxic T Lymphocyte (CTL) Epitopes for the Study of CTL Escape, Functional Avidity and Viral Evolution</b>		II-B-15	Pol CTL/CD8+ epitopes . . . . . 496
<i>Nicole Frahm, Brett Baker, Christian Brander</i>		II-B-16	Vif CTL/CD8+ epitopes . . . . . 502
I-A-1 Associations between T cell specificity and viral control: cause or effect? . . . . .	3	II-B-17	Vpr CTL/CD8+ epitopes . . . . . 518
I-A-2 The role of functional avidity in the control of highly variable pathogens . . . . .	3	II-B-18	Tat CTL/CD8+ epitopes . . . . . 534
I-A-3 Refined HLA footprint analyses and the identification of novel CTL epitopes and HLA binding motifs . . . . .	4	II-B-19	Rev CTL/CD8+ epitopes . . . . . 549
I-A-4 Are current criteria for the definition of “optimal” epitopes helpful to the community . . . . .	4	II-B-20	Vpu CTL/CD8+ epitopes . . . . . 564
I-A-5 Table of optimal HIV-1 CTL epitopes . . . . .	5	II-B-21	gp160 CTL/CD8+ epitopes . . . . . 567
I-A-6 Map of optimal HIV-1 CTL epitopes . . . . .	13	II-B-22	Env CTL/CD8+ epitopes . . . . . 698
I-A-7 Acknowledgments . . . . .	18	II-B-23	Nef CTL/CD8+ epitopes . . . . . 712
I-A-8 References . . . . .	18	II-B-24	HIV-1 CTL/CD8+ epitopes . . . . . 874
		<b>II-C</b>	<b>Maps of CTL/CD8+ Epitope Locations Plotted by Protein 891</b>
<b>Part II. HIV CTL CD8+ Epitopes</b>	<b>25</b>	II-C-1	p17 CTL/CD8+ Epitope Map . . . . . 892
<b>II-A Summary</b>	<b>27</b>	II-C-2	p24 CTL/CD8+ Epitope Map . . . . . 894
II-A-1 Epitope tables . . . . .	27	II-C-3	p2p7p1p6 CTL/CD8+ Epitope Map . . . . . 896
II-A-2 HIV protein epitope maps . . . . .	28	II-C-4	Gag/Pol TF CTL/CD8+ Epitope Map . . . . . 897
II-A-3 Alignments . . . . .	28	II-C-5	Protease CTL/CD8+ Epitope Map . . . . . 897
<b>II-B HIV CTL/CD8+ Epitope Tables</b>	<b>29</b>	II-C-6	RT CTL/CD8+ Epitope Map . . . . . 897
II-B-1 Gag p17 CTL/CD8+ epitopes . . . . .	29	II-C-7	Integrase CTL/CD8+ Epitope Map . . . . . 899
II-B-2 Gag p17-p24 CTL/CD8+ epitopes . . . . .	122	II-C-8	Vif CTL/CD8+ Epitope Map . . . . . 900
II-B-3 Gag p24 CTL/CD8+ epitopes . . . . .	124	II-C-9	Vpr CTL/CD8+ Epitope Map . . . . . 900
		II-C-10	Tat CTL/CD8+ Epitope Map . . . . . 901
		II-C-11	Rev CTL/CD8+ Epitope Map . . . . . 901
		II-C-12	Vpu CTL/CD8+ Epitope Map . . . . . 901
		II-C-13	gp160 CTL/CD8+ Epitope Map . . . . . 902
		II-C-14	Nef CTL/CD8+ Epitope Map . . . . . 906
		<b>Part III. HIV Helper CD4+ T-Cell Epitopes</b>	<b>911</b>
		<b>III-A Summary</b>	<b>913</b>
		III-A-1	Epitope tables . . . . . 913
		III-A-2	HIV protein epitope maps . . . . . 914
		III-A-3	Alignments . . . . . 914

## Contents

<b>III-B HIV Helper/CD4+ T-Cell Epitope Tables</b>	<b>915</b>	IV-B-3	MABs by order of appearance in tables	1107	
III-B-1	Gag p17 Helper/CD4+ T-cell epitopes	915	<b>IV-C HIV Antibodies Tables</b>	<b>1115</b>	
III-B-2	Gag p17-p24 Helper/CD4+ T-cell epitopes . . . . .	923	IV-C-1	Gag p17 Antibodies . . . . .	1115
III-B-3	Gag p24 Helper/CD4+ T-cell epitopes	923	IV-C-2	Gag p17-p24 Antibodies . . . . .	1120
III-B-4	Gag p2p7p1p6 Helper/CD4+ T-cell epitopes . . . . .	955	IV-C-3	Gag p24 Antibodies . . . . .	1120
III-B-5	Gag Helper/CD4+ T-cell epitopes . .	960	IV-C-4	Gag p24-p2p7p1p6 Antibodies . . .	1132
III-B-6	Protease Helper/CD4+ T-cell epitopes	971	IV-C-5	Gag p2p7p1p6 Antibodies . . . . .	1132
III-B-7	RT Helper/CD4+ T-cell epitopes . .	972	IV-C-6	Gag Antibodies . . . . .	1133
III-B-8	RT-Integrase Helper/CD4+ T-cell epitopes . . . . .	980	IV-C-7	Protease Antibodies . . . . .	1140
III-B-9	Integrase Helper/CD4+ T-cell epitopes	980	IV-C-8	RT Antibodies . . . . .	1142
III-B-10	Pol Helper/CD4+ T-cell epitopes . .	983	IV-C-9	Integrase Antibodies . . . . .	1144
III-B-11	Vif Helper/CD4+ T-cell epitopes . .	984	IV-C-10	Pol Antibodies . . . . .	1148
III-B-12	Vpr Helper/CD4+ T-cell epitopes . .	985	IV-C-11	Vif Antibodies . . . . .	1154
III-B-13	Tat Helper/CD4+ T-cell epitopes . .	986	IV-C-12	Vpr Antibodies . . . . .	1154
III-B-14	Rev Helper/CD4+ T-cell epitopes . .	989	IV-C-13	Tat Antibodies . . . . .	1154
III-B-15	Vpu Helper/CD4+ T-cell epitopes . .	991	IV-C-14	Rev Antibodies . . . . .	1164
III-B-16	gp160 Helper/CD4+ T-cell epitopes	992	IV-C-15	Vpu Antibodies . . . . .	1166
III-B-17	Env Helper/CD4+ T-cell epitopes . .	1054	IV-C-16	gp160 Antibodies . . . . .	1166
III-B-18	Nef Helper/CD4+ T-cell epitopes . .	1063	IV-C-17	Env Antibodies . . . . .	1315
III-B-19	HIV-1 Helper/CD4+ T-cell epitopes	1075	IV-C-18	Nef Antibodies . . . . .	1505
			IV-C-19	HIV-1 Antibodies . . . . .	1515
<b>III-C Maps of T-Helper/CD4+ Epitope Locations Plotted by Protein</b>	<b>1083</b>	<b>IV-D Maps of MAb Locations Plotted by Protein</b>	<b>1523</b>		
III-C-1	p17 T-Helper/CD4+ Epitope Map . .	1083	IV-D-1	p17 Ab Epitope Map . . . . .	1523
III-C-2	p24 T-Helper/CD4+ Epitope Map . .	1083	IV-D-2	p24 Ab Epitope Map . . . . .	1524
III-C-3	p2p7p1p6 T-Helper/CD4+ Epitope Map . . . . .	1084	IV-D-3	p2p7p1p6 Ab Epitope Map . . . . .	1525
III-C-4	Gag/Pol TF T-Helper/CD4+ Epitope Map . . . . .	1085	IV-D-4	Gag/Pol TF Ab Epitope Map . . . . .	1525
III-C-5	Protease T-Helper/CD4+ Epitope Map	1085	IV-D-5	Protease Ab Epitope Map . . . . .	1525
III-C-6	RT T-Helper/CD4+ Epitope Map . .	1085	IV-D-6	RT Ab Epitope Map . . . . .	1525
III-C-7	Integrase T-Helper/CD4+ Epitope Map	1086	IV-D-7	Integrase Ab Epitope Map . . . . .	1526
III-C-8	Vif T-Helper/CD4+ Epitope Map . .	1086	IV-D-8	Vif Ab Epitope Map . . . . .	1526
III-C-9	Vpr T-Helper/CD4+ Epitope Map . .	1086	IV-D-9	Vpr Ab Epitope Map . . . . .	1526
III-C-10	Tat T-Helper/CD4+ Epitope Map . .	1086	IV-D-10	Tat Ab Epitope Map . . . . .	1526
III-C-11	Rev T-Helper/CD4+ Epitope Map . .	1087	IV-D-11	Rev Ab Epitope Map . . . . .	1527
III-C-12	Vpu T-Helper/CD4+ Epitope Map . .	1087	IV-D-12	Vpu Ab Epitope Map . . . . .	1527
III-C-13	gp160 T-Helper/CD4+ Epitope Map	1087	IV-D-13	gp160 Ab Epitope Map . . . . .	1527
III-C-14	Nef T-Helper/CD4+ Epitope Map . .	1090	IV-D-14	Nef Ab Epitope Map . . . . .	1534
<b>Part IV. HIV Antibody Binding Sites</b>	<b>1091</b>	<b>Part V. HIV Immunology References</b>	<b>1535</b>		
<b>IV-A Summary</b>	<b>1093</b>				
IV-A-1	Indices . . . . .	1093			
IV-A-2	Tables . . . . .	1093			
IV-A-3	HIV protein binding site maps . . .	1094			
IV-A-4	Alignments . . . . .	1094			
<b>IV-B Cross Reference Listing of MABs</b>	<b>1095</b>				
IV-B-1	MABs by binding type . . . . .	1095			
IV-B-2	Alphabetical listing of MABs . . . .	1100			



# Preface

## Scope and purpose of the HIV molecular immunology database

*HIV Molecular Immunology* is a companion volume to *HIV Sequence Compendium*. This publication, the 2008 edition, is the PDF version, suitable for printing, of the web-based HIV Immunology Database (<http://www.hiv.lanl.gov/content/immunology/>). The web interface for this relational database has many search options, as well as interactive tools to help immunologists design reagents and interpret their results.

In the HIV Immunology Database, HIV-specific B-cell and T-cell responses are summarized and annotated. Immunological responses are divided into three parts, CTL, T helper, and antibody. Within these parts, defined epitopes are organized by protein and binding sites within each protein, moving from left to right through the coding regions spanning the HIV genome. We include human responses to natural HIV infections, as well as vaccine studies in a range of animal models and human trials. Responses that are not specifically defined, such as responses to whole proteins or monoclonal antibody responses to discontinuous epitopes, are summarized at the end of each protein section. Studies describing general HIV responses to the virus, but not to any specific protein, are included at the end of each part.

The annotation includes information such as cross-reactivity, escape mutations, antibody sequence, TCR usage, functional domains that overlap with an epitope, immune response associations with rates of progression and therapy, and how specific epitopes were experimentally defined. Basic information such as HLA specificities for T-cell epitopes, isotypes of monoclonal antibodies, and epitope sequences are included whenever possible. All studies that we can find that incorporate the use of a specific monoclonal antibody are included in the entry for that antibody. A single T-cell epitope can have multiple entries, generally one entry per study.

Finally, maps of all defined linear epitopes relative to the HXB2 reference proteins are provided. Alignments of CTL, helper T-cell, and antibody epitopes are available through the search interface on our web site at <http://www.hiv.lanl.gov/content/immunology>.

Only responses to HIV-1 and HIV-2 are included in the database. CTL responses to SIVs are periodically summarized in our review section by Dr. David Watkins and colleagues. Dr. Christian Brander and colleagues annually provide a concise listing of optimally defined CTL epitopes. Reviews from previous years can

be found at <http://www.hiv.lanl.gov/content/sequence/HIV/REVIEWS/reviews.html>.

Questions regarding the database can be sent via email to [immuno@lanl.gov](mailto:immuno@lanl.gov).

## About the data

At the time of this publication, the HIV Immunology Database contained over 4900 CTL/CD8+ epitopes, over 1000 Helper/CD4+ epitopes, over 1400 unique antibody epitopes, and a total bibliography of over 2100 references (Figure 1). To illustrate the distribution of the epitopes, we have plotted them by position in the HIV proteome (Figure 2).

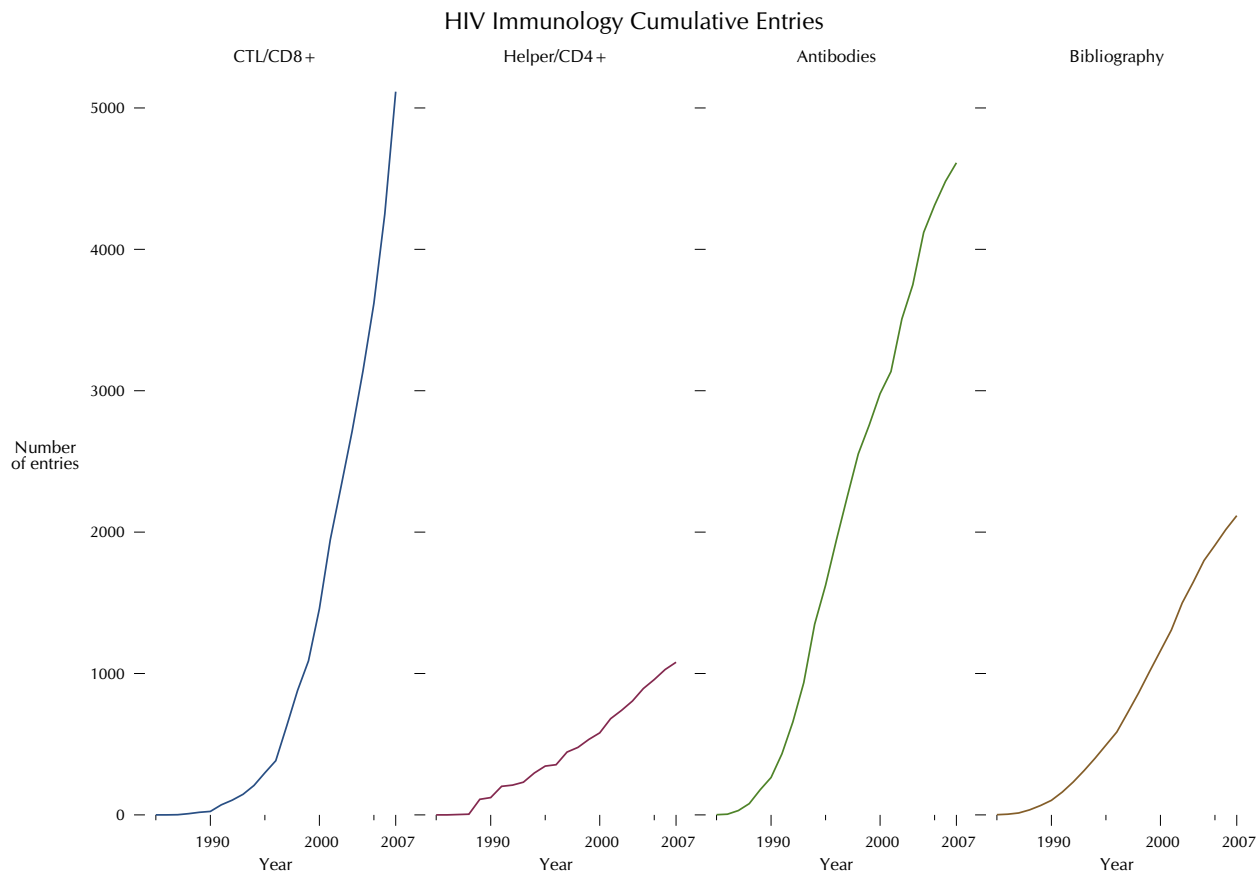
For T-cell epitopes, the density of epitopes by position reflects the density of defined epitopes in the database, which in turn roughly reflects the density of responses, as judged by EliSpot assays from natural infection. Both CTL/CD8+ T-cell (maroon) and Helper/CD4+ T-cell (green) responses are most commonly detected in Gag and Nef, and the database has the highest density of epitopes captured from the literature in these regions.

In contrast, the antibody epitope database density (blue) is less meaningfully captured in this graph, because only continuous epitopes are included. Many antibody responses defined in the database are to discontinuous epitopes, or are defined regionally or by competition experiments, and other database entries are polyclonal responses with multiple antibodies binding to multiple regions; these are not included in this map. The database entries have other biases in frequency. For example, the database is based on retrieval of information from the literature, and so a region like the V3 loop of HIV-1, which is of particular interest to investigators, has been studied with great intensity, and this high level of interest accounts for the large spike of antibody entries in gp120.

## Citing the database

This publication may be cited as

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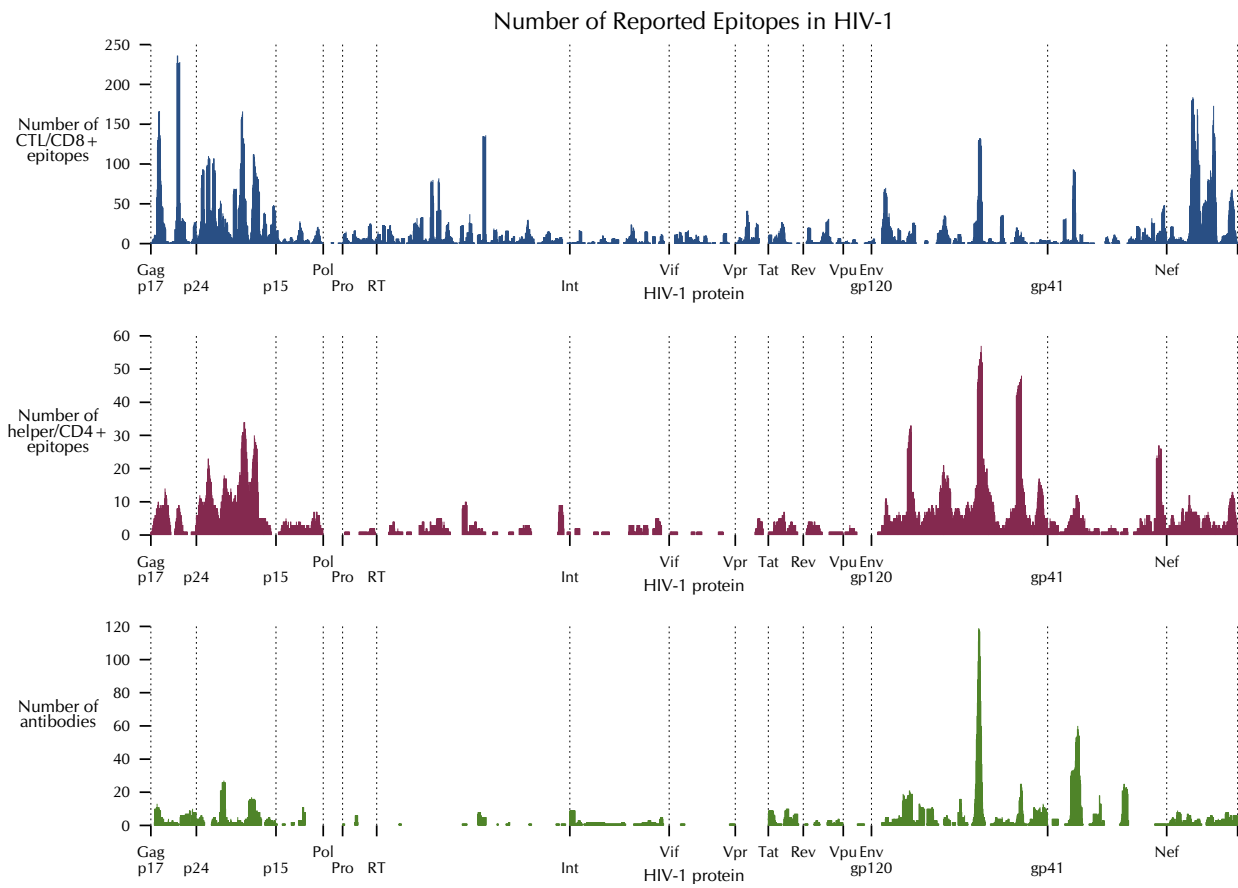


**Figure 1:** HIV immunology database cumulative entries. The CTL, T Helper and Antibodies plots show the total number of epitope entries described in the database at the denoted point in time. If an epitope is described in 5 papers then it is considered to be 5 entries. Thus the number of unique epitopes is lower than the plotted number. Although all 4 plots begin at 1985, the earliest CTL and Helper epitopes were described in 1987.

## About the PDF

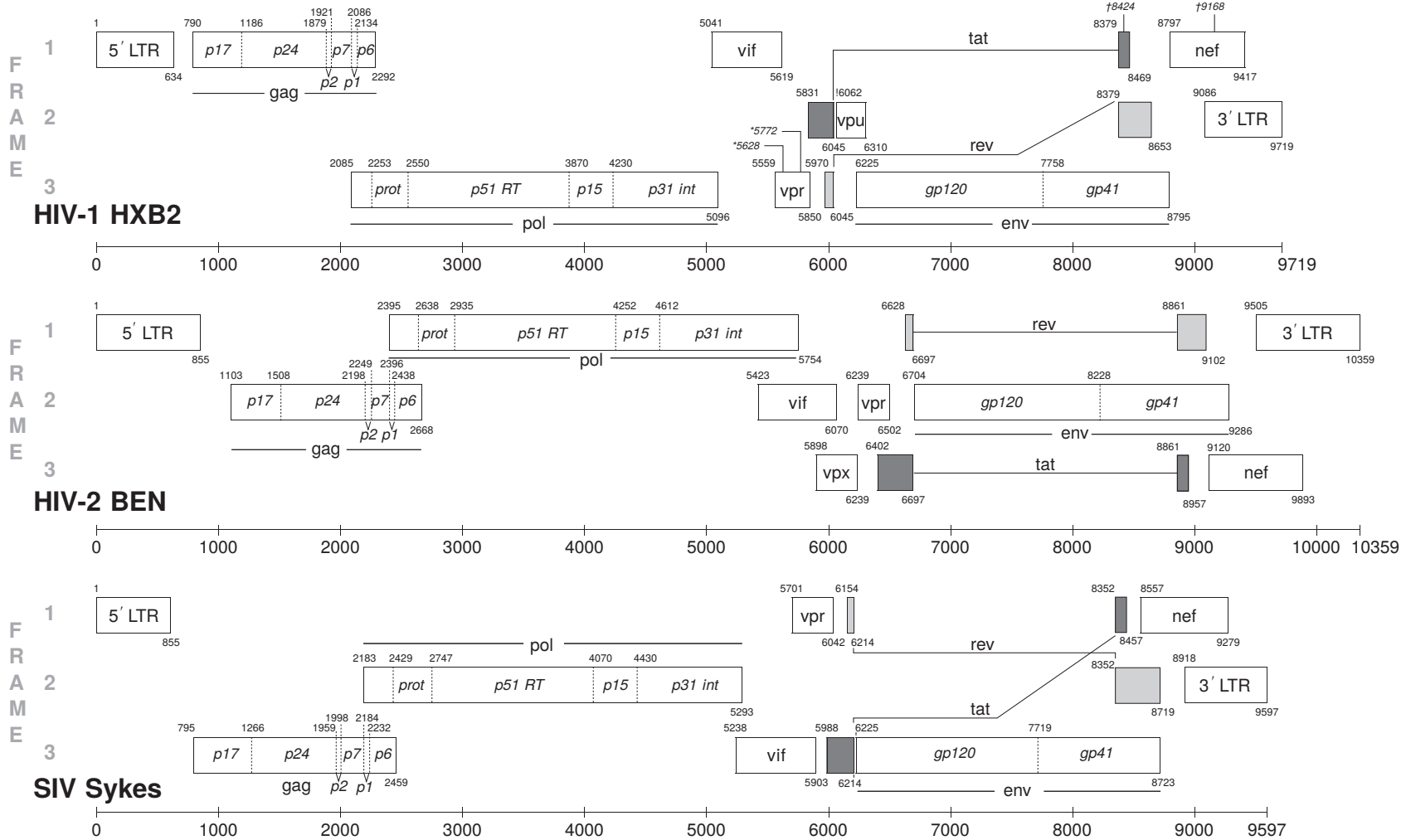
The complete *HIV Molecular Immunology 2008* is available in Adobe Portable Document Format (PDF) from our website, <http://www.hiv.lanl.gov/content/immunology>. The PDF version is hypertext enabled and features 'clickable' table-of-contents, indexes, references and links to external web sites.

This volume is typeset using  $\text{\LaTeX}$ . The immunology data tables and epitope maps are produced automatically from the SQL database by a series of Perl programs.



**Figure 2:** The number of unique epitopes included in the database that span each position in the HIV proteome.

## Genome maps



**Landmarks of the HIV-1, HIV-2, and SIV genomes.** The gene start, indicated by the small number in the upper left corner of each rectangle, normally records the position of the a in the atg start codon for that gene while the number in the lower right records the last position of the stop codon. For *pol*, the start is taken to be the first t in the sequence ttttttag which forms part of the stem loop that potentiates ribosomal slippage on the RNA and a resulting -1 frameshift and the translation of the Gag-Pol polyprotein. The *tat* and *rev* spliced exons are shown as shaded rectangles. In HXB2, \*5628 and \*5772 mark positions of frameshifts in the *vpr* gene; †6062 indicates a defective acg start codon in *vpu*; †8424 and †9168 mark premature stop codons in *tat* and *nef*. See Korber *et al.*, Numbering Positions in HIV Relative to HXB2CG, in *Human Retroviruses and AIDS*, 1998, p. 102. Available from <http://www.hiv.lanl.gov/content/sequence/HIV/REVIEWS/HXB2.html>

## HIV/SIV proteins

Name	Size	Function	Localization
Gag MA	p17	membrane anchoring; env interaction; nuclear transport of viral core (myristylated protein)	virion
CA	p24	core capsid	virion
NC	p7	nucleocapsid, binds RNA	virion
	p6	binds Vpr	virion
Protease (PR)	p15	gag/pol cleavage and maturation	virion
Reverse Transcriptase (RT)	p66, p51	reverse transcription	virion
RNase H	(heterodimer)	RNase H activity	virion
Integrase (IN)		DNA provirus integration	virion
Env	gp120/gp41	external viral glycoproteins bind to CD4 and chemokine co-receptors	plasma membrane, virion envelope
Tat	p16/p14	viral transcriptional transactivator	primarily in nucleolus/nucleus
Rev	p19	RNA transport, stability and utilization factor (phosphoprotein)	primarily in nucleolus/nucleus shuttling between nucleolus and cytoplasm
Vif	p23	viral infectivity factor, inhibits minus-strand viral DNA hypermutation	cytoplasm (cytosol, membranes), virion
Vpr	p10-15	promotes nuclear localization of preintegration complex, inhibits cell division, arrests infected cells at G2/M	virion nucleus (nuclear membrane?)
Vpu	p16	promotes extracellular release of viral particles; degrades CD4 in the ER; (phosphoprotein only in HIV-1 and SIVcpz)	integral membrane protein
Nef	p27-p25	CD4 and class I downregulation (myristylated protein)	plasma membrane, cytoplasm, (virion?)
Vpx	p12-16	Vpr homolog present in HIV-2 and some SIVs, absent in HIV-1	virion (nucleus?)
Tev	p28	tripartite tat-env-rev protein (also named Tnv)	primarily in nucleolus/nucleus

## Abbreviations

Abbreviations and acronyms used in this database.

Abbrev.	Meaning
AA	amino acid
AAV	adeno-associated virus
Ab	antibody
ACTG	AIDS clinical trial group
ADC	AIDS dementia complex
ADCC	antibody-dependent cell-mediated cytotoxicity
ADE	antibody-dependent enhancement
ADRA	Antiviral Drug Resistance Analysis: a program that analyzes your sequences for mutations known to confer drug resistance and links to the records in the database
AIDS	acquired immunodeficiency syndrome
ANN	artificial neural networks
APC	antigen presenting cell
ARC	AIDS related complex
ART	anti-retroviral therapy
AZT	azidothymidine
BIMAS	BioInformatics and Molecular Analysis Section
BIV	bovine immunodeficiency virus
BLAST	Basic Local Alignment Search Tool
CAEV	caprine arthritis/encephalitis virus
CD4BS	CD4 binding site
CD4i	antibody that has enhanced binding to gp120 in the presence of SCD4 (CD4 induced)
CDC	Centers for Disease Control and Prevention
CDR	complementary determining regions
CFA	complete Freund's adjuvant
CHI	Center for HIV Information
CMI	cell-mediated immunity
CMV	cytomegaliovirus
CNS	central nervous system
CP	canary pox
CRF	circulating recombinant form
CsA	cyclosporine A
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
CTL <sub>e</sub>	CTL effector
CTL <sub>p</sub>	CTL precursor
CyPA	cyclophilin A
DC	dendritic cell
DDDP	DNA-dependent DNA polymerase
DHH	U. S. Department of Health and Human Services
dMM	deopymannojirimycin
dpc	days post challenge
DTT	dithiothrietol

Abbrev.	Meaning
EIA	enzyme immuno assay
EIAV	equine infectious anemia virus
ELF	Epitope Location Finder
ELISA	Enzyme Linked ImmunoSorbent Assay
ER	endoplasmic reticulum
Fabs	fragment antigen binding-univalent antibody fragment
FATT-CTL	Fluorescent antigen-transfected target cell-CTL
FIV	feline immunodeficiency virus
FP	fowl pox
FSW	female sex worker
GALT	gut-associated lymphoid tissues
GDE format	Genetic Data Environment
gp	glycoprotein
GRIV	genetic resistance to HIV
HAART	highly-active anti-retroviral therapy
HCV	hepatitis C virus
HEPS	HIV-exposed persistently seronegative
HIV	human immunodeficiency virus
HIVD	HIV-1 dementia
HLA	human leukocyte antigens
HLA-MHC	human leukocyte antigens-major histocompatibility complex
HMM	hidden Markov models
IAVI	International AIDS Vaccine Initiative
IDE	immunodominant epitope
IE genes	immediate early genes
IFA	incomplete Freund's adjuvant
IFN	interferon
IG format	IntelliGenetics format
Ig	immunoglobulin
IL	interleukin
INHI	immunologically normal HIV-infected
iscom	immunostimulating complex
KLH	keyhole limpet hemocyanin
LANL	Los Alamos National Laboratory
LDA	limiting dilution assay
LN	lymph node
LPR	lymphoproliferative response
LT	labile enterotoxin
LTNP	long-term non-progressor
LTR	long terminal repeat
LTS	long term survivor
mAb	monoclonal antibody
MBL	mannose-binding lectin
MCMC	Markov chain Monte Carlo
MDP	muramyl dipeptide
MEI	multiple epitope immunogen
MHC	major histocompatibility complex
MHR	major homology region
ML	maximum likelihood
MLV	murine leukemia virus

Abbrev.	Meaning
MP	maximum parsimony
mpc	months post challenge
MPER	membrane-proximal external region
MRC	Medical Research Council, UK
MSF	multiple sequence alignment format of the GCG sequence analysis package
MV	measles vector
MVA vector	modified vaccinia virus Ankara
Nab	neutralizing antibody
NCBI	National Center for Biotechnology Information
NIAID	National Institute of Allergies and Infectious Diseases
NIBSC	National Institute for Biological Standards and Control, UK
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology
NJ	neighbor joining
NLS	nuclear localization signal
NRP	non-rapid progressor
NSI	non-synctium-inducing protein
p	protein
PB	peripheral blood
PBL	peripheral blood lymphocyte
PBMC	peripheral blood mononuclear cell
PCOORD	principal coordinate analysis
PCR	polymerase chain reaction
PERV	porcine endogenous retrovirus
PHYLP	Phylogeny Inference Package
PL	proteoliposome
RAC	ricin A chain
RDDP	RNA-dependent DNA polymerase
rec/r	recombinant
RIP	Recombinant Identification Program: a program for detecting evidence of inter-subtype recombination
RIPA	Radio Immuno Precipitation Assay
RP	rapid progressor
RRE	Rev-responsive element
rsgp160	recombinant soluble gp160
RSV	Rous sarcoma virus
SAM	Sequence Alignment and Modeling program
SAP	sequential antigen panning
sCD4	soluble CD4
scFv	single-chain variable fragment
SDS	sodium dodecyl sulfate
SFV	Semliki Forest virus
SI	synctium inducing
SIV	simian immunodeficiency virus

Abbrev.	Meaning
SIVE	SIV encephalitis
SLE	systemic lupus erythematosis
SNAP	synonymous-nonsynonymous analysis program
STI	supervised treatment interruption (also seen as structured treatment interruption and standard treatment interruption)
TCLA	T cell line adapted
TCR	T-cell receptor
Th	T-helper cell
TNF	tumor necrosis factor
VEE	Venezuelan equine encephalitis
VESPA	Viral Epidemiology Signature Pattern Analysis
VIP	vasoactive intestinal peptide
VL	viral load
VLP	virus like particle, assembled from p55 gag
VSV	vesicular stomatitis virus
VV	vaccinia virus
WB	Western Blot

### Amino Acid Codes

A	Alanine
B	Aspartic Acid or Asparagine
C	Cysteine
D	Aspartic Acid
E	Glutamic Acid
F	Phenylalanine
G	Glycine
H	Histidine
I	Isoleucine
K	Lysine
L	Leucine
M	Methionine
N	Asparagine
P	Proline
Q	Glutamine
R	Arginine
S	Serine
T	Threonine
V	Valine
W	Tryptophan
X	unknown or "other" amino acid
Y	Tyrosine
Z	Glutamic Acid or Glutamine
.	gap
-	identity
\$	stop codon
#	frameshift





**Part I**  
**Review Articles**



## I-A

# Identification and Optimal Definition of HIV-Derived Cytotoxic T Lymphocyte (CTL) Epitopes for the Study of CTL Escape, Functional Avidity and Viral Evolution

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## I-A-1 Associations between T cell specificity and viral control: cause or effect?

Despite ongoing efforts into the characterization of immune correlates of controlled HIV infection, the impact of antigen specificity, viral sequence variation and variant cross-recognition on the control of viral replication and HIV disease progression remains unknown. While a steadily growing number of reports confirm the association between T cell responses directed against the HIV Gag protein and reduced viral load [Zuñiga *et al.*, 2006; Brumme *et al.*, 2008; Kiepiela *et al.*, 2007; Masemola *et al.*, 2004a; Rolland *et al.*, 2008], and despite some reports showing a rapid re-presentation of Gag-derived antigen from the incoming virus [Sacha *et al.*, 2007], it remains unclear whether a) these associations reflect the cause or the consequences of otherwise controlled infection and b) whether, and if so, which regions outside of Gag would present effective targets of the host cellular immune response to HIV. Similarly, although a number of recent reports have established strong associations between reduced viral replicative fitness and specific viral sequence changes in Gag epitopes restricted by HLA alleles associated with relative protection [Brockman *et al.*, 2007; Schneidewind *et al.*, 2007; Martinez-Picado *et al.*, 2006], these analyses urgently need to be expanded to other, broadly distributed HLA alleles and targets located in viral proteins other than Gag. In addition, the consequences of sequence variation on T cell recognition, often assumed to reflect effective T cell escape,

will need to be more carefully assessed, ideally including approaches such as viral inhibition assays and testing for different T cell effector functions to discriminate between partial agonistic variants, antagonistic or superagonistic sequence changes, or true CTL escape due to abrogated HLA binding, missing TCR interaction or severely impaired antigen processing.

## I-A-2 The role of functional avidity in the control of highly variable pathogens

A rapidly growing number of reports have also started to assess the role of T cell receptor repertoire diversity, TCR functional avidity and variant recognition [Price *et al.*, 2005; Turnbull *et al.*, 2006; Messaoudi *et al.*, 2002]. Recently published data in HCV infection has linked the presence of T cell responses of high functional avidity with a superior ability to cross-react with sequence variants [Yerly *et al.*, 2008]. Although these high avidity HCV-specific T cell populations were mainly found in subjects that spontaneously cleared HCV infection, it remains unclear whether individuals who went on to become chronically infected initially also had such high avidity responses which, for unknown reasons, got lost over time, similarly to what has recently been described in longitudinal analyses in HIV infection. Emerging data in HIV infection confirms the analyses in HCV as Frahm *et al.* (unpublished data) and likely others have identified particularly highly avid and broadly cross-reactive T cell populations in HIV controllers, but less so in individuals with progressive HIV disease. It thus appears likely that an effective HIV vaccine (and HCV, too) would likely profit from the induction of such high avidity responses.

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### I-A-3 Refined HLA footprint analyses and the identification of novel CTL epitopes and HLA binding motifs

Aside from determining the roles of functional avidity and TCR repertoires, the analysis of viral evolution as a consequence of cytotoxic T lymphocyte (CTL) mediated immune pressure has given rise to a flurry of publications over the last few years [Moore *et al.*, 2002; McMichael & Klenerman, 2002]. Since the initial description of these HLA footprints in the HIV sequence, refined approaches have now been developed that take into consideration potentially confounding effects of the phylogeny of the analyzed sequences and HLA linkage disequilibrium [Brumme *et al.*, 2008; Bhattacharya *et al.*, 2007; Brumme *et al.*, 2007]. These analyses have also allowed for the identification of novel T cell epitopes by a sort of a “reversed” genetic approach that points towards the existence of novel T cell epitopes at or close to sites of strong associations between specific HLA alleles and recurrent viral sequence polymorphisms. With larger cohorts being generated and comprehensively analyzed in different geographic regions of the world with populations of considerably different host genetics and circulating viral populations, such HLA footprint analyses now also allow to assess the global effects of viral adaptation to HLA restricted T cell mediated immune pressure [Rousseau *et al.*, 2008]. Taking into consideration the balancing effects of forward mutations and reversion to pre-infection sequence, large cohort based analyses, together with detailed *in vitro* viral fitness studies, may also allow to determine the relative strength of the CTL mediated immune pressure and the effectiveness of an epitope specific CTL response. Especially for these kinds of studies, however, it is necessary to define the precise epitope so that the effectiveness of CTL escape and its potential different mechanisms (processing escape versus abrogated HLA binding, etc.) can correctly be assessed.

With more studies moving into populations where less well-characterized HLA alleles are more prevalent, epitope definition becomes more difficult (due to less well known binding motifs for instance) but also more informative for the relevant populations. Especially for such less well characterized alleles, the inference of binding motifs and subsequent identification of optimal epitopes through the analysis of HLA sequence positions lining the binding pockets has proven quite effective [Honeyborne *et al.*, 2007; Frahm *et al.*, 2005, 2006]. At the same time, our own analyses on promiscuously presented HIV epitopes clearly indicate that the current description of allele-specific motifs is still incomplete, and that the identification of truly optimally defined epitopes, viral or not, will help to amend and more accurately define existing binding motifs [Frahm *et al.*, 2007]. This would obviously

not only facilitate the work in HIV but also in other viral infections, cancer and autoimmunity.

### I-A-4 Are current criteria for the definition of “optimal” epitopes helpful to the community

As in past years, the present listing is based on the inclusion of epitopes that fulfill a number of criteria intended to ensuring reliable description of the optimal length epitope and correct assignment of the restricting HLA class I allele(s) [Brander & Walker, 1995, 1996]. Nevertheless, there may still be occasions where the data reported here conflict with data in other laboratories and we would like to encourage any investigator who observes discrepancies in his/her own data with what is reported here to bring this to our attention. In addition, we have still adhered to the previously described inclusion criteria, being aware that some epitopes may fail one or more of these tests although they may indeed represent optimal epitopes [Schellens *et al.*, 2008; Mueller *et al.*, 2007]. In particular, we and others are moving towards the use of single HLA allele transfected cell lines for HLA restriction analyses. While this approach would seemingly define the presenting allele directly, it is possible that stabilization of the allele on the cell surface may be sufficient to trigger a response, even though the allele is not the truly restricting one. We would thus like to suggest that each class I allele expressed by the subject from whom the effector cells were obtained be tested, either as single allele expressing cell lines or as a negative control antigen presenting cell line that matches as many of the presumably non-restricting alleles as possible. Alternatively, a known good binding epitope different from the one that is to be mapped could be used to exclude unspecific reaction due to high peptide concentration in the assay. High peptide concentration may also be a factor for the elicitation of responses in the Elispot assay that are however unable to inhibit viral replication [Valentine *et al.*, 2008]. While such cases may indeed identify epitopes with likely little contribution to effective viral control *in vivo*, their identification is still necessary to allow for their exclusion from potential immunogen sequences.

## I-A-5 Table of optimal HIV-1 CTL epitopes

Table I-A.1: Best defined HIV CTL epitopes.

HLA	Protein	AA	Sequence	Reference
A*0101 (A1)	gp160	787–795	RRGWEVLKY	Cao, 2002
A2	RT	127–135	YTAFTIPSV	Draenert <i>et al.</i> , 2004b
A*0201 (A2)	p17	77–85	SLYNTVATL	Johnson <i>et al.</i> , 1991; Parker <i>et al.</i> , 1992, 1994
A*0201 (A2)	p2p7p1p6	70–79	FLGKIWPSYK	Yu <i>et al.</i> , 2002b
A*0201 (A2)	Protease	76–84	LVGPTPVNI	Karlsson <i>et al.</i> , 2003
A*0201 (A2)	RT	33–41	ALVEICTEM	Haas <i>et al.</i> , 1998; Haas, 1999
A*0201 (A2)	RT	179–187	VIYQYRDDL	Harrer <i>et al.</i> , 1996a
A*0201 (A2)	RT	309–317	ILKEPVHGV	Walker <i>et al.</i> , 1989; Tsomides <i>et al.</i> , 1991
A*0201 (A2)	Vpr	59–67	AIIRILQQL	Altfeld <i>et al.</i> , 2001a,b
A*0201 (A2)	gp160	311–320	RGPGRFVVI	Alexander-Miller <i>et al.</i> , 1996
A*0201 (A2)	gp160	813–822	SLLNATDIAV	Dupuis <i>et al.</i> , 1995
A*0201 (A2)	Nef	136–145	PLTFGWICYKL	Haas <i>et al.</i> , 1996; Maier & Autran, 1999
A*0201 (A2)	Nef	180–189	VLEWRFDLRL	Haas <i>et al.</i> , 1996; Maier & Autran, 1999
A*0202 (A2)	p17	77–85	SLYNTVATL	Goulder, 1999
A*0205 (A2)	p17	77–85	SLYNTVATL	Goulder, 1999
A*0205 (A2)	gp160	846–854	RIRQLERA	Sabbaj <i>et al.</i> , 2003
A*0205 (A2)	Nef	83–91	GAFDLSFFL	Rathod, 2006
A*0207 (A2)	p24	164–172	YVDRFYKTL	Currier <i>et al.</i> , 2002
A*0301 (A3)	p17	18–26	KIRLRPGGK	Harrer <i>et al.</i> , 1996b
A*0301 (A3)	p17	20–28	RLRPGGKKK	Goulder <i>et al.</i> , 1997b; Culmann, 1999; Lewinsohn & Riddell, 1999; Wilkes & Ruhl, 1999
A*0301 (A3)	p17	20–29	RLRPGGKKKY	Goulder <i>et al.</i> , 2000b
A*0301 (A3)	RT	33–43	ALVEICTEMEK	Haas <i>et al.</i> , 1998; Haas, 1999
A*0301 (A3)	RT	73–82	KLVDLFRELNK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	RT	93–101	GIPHPAGLK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	RT	158–166	AIFQSSMTK	Threlkeld <i>et al.</i> , 1997
A*0301 (A3)	RT	269–277	QIYPGIKVR	Yu <i>et al.</i> , 2002a
A*0301 (A3)	RT	356–366	RMRGAHTNDVK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	Integrase	179–188	AVFIHNFKRK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	Vif	17–26	RIRTWKSLVK	Altfeld <i>et al.</i> , 2001a; Yu <i>et al.</i> , 2002a
A*0301 (A3)	Vif	28–36	HMYISKKAK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	Vif	158–168	KTKPPLPSVKK	Yu <i>et al.</i> , 2002a
A*0301 (A3)	Rev	57–66	ERILSTYLGR	Addo, 2002; Yu <i>et al.</i> , 2002a
A*0301 (A3)	gp160	37–46	TVYYGVPVWK	Johnson <i>et al.</i> , 1994
A*0301 (A3)	gp160	770–780	RLRDLILLIVTR	Takahashi <i>et al.</i> , 1991
A*0301 (A3)	Nef	73–82	QVPLRPMYTK	Koenig <i>et al.</i> , 1990; Culmann <i>et al.</i> , 1991
A*0301 (A3)	Nef	84–92	AVDLSHFLK	Yu <i>et al.</i> , 2002a

Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
A*1101 (A11)	p17	84–91	TLYCVHQK	Harrer <i>et al.</i> , 1998
A*1101 (A11)	p24	217–227	ACQGVGGPGHK	Sipsas <i>et al.</i> , 1997
A*1101 (A11)	RT	158–166	AIFQSSMTK	Johnson & Walker, 1994; Zhang <i>et al.</i> , 1993; Threlkeld <i>et al.</i> , 1997
A*1101 (A11)	RT	341–350	IYQEPFKNLK	Culmann, 1999
A*1101 (A11)	RT	520–528	QIIEQLIKK	Fukada <i>et al.</i> , 1999
A*1101 (A11)	Integrase	179–188	AVFIHNFKRK	Fukada <i>et al.</i> , 1999
A*1101 (A11)	Integrase	203–211	IIATDIQTK	Wang <i>et al.</i> , 2007
A*1101 (A11)	gp160	199–207	SVITQACPK	Fukada <i>et al.</i> , 1999
A*1101 (A11)	Nef	73–82	QVPLRPMTYK	Buseyne, 1999
A*1101 (A11)	Nef	75–82	PLRPMTYK	Culmann <i>et al.</i> , 1991
A*1101 (A11)	Nef	84–92	AVDLSHFLK	Culmann <i>et al.</i> , 1991
A23	gp160	585–593	RYLKDQQLL	Cao <i>et al.</i> , 2003
A*2402 (A24)	p17	28–36	KYKLGKHIW	Ikeda-Moore <i>et al.</i> , 1998; Lewinsohn, 1999
A*2402 (A24)	p24	162–172	RDYVDRFFKTL	Dorrell <i>et al.</i> , 1999; Rowland-Jones, 1999
A*2402 (A24)	gp160	52–61	LFCASDAKAY	Lieberman <i>et al.</i> , 1992; Shankar <i>et al.</i> , 1996
A*2402 (A24)	gp160	585–593	RYLKDQQLL	Dai <i>et al.</i> , 1992
A*2402 (A24)	Nef	134–141	RYPLTFGW	Goulder <i>et al.</i> , 1997a; Ikeda-Moore <i>et al.</i> , 1998
A*2501 (A25)	p24	13–23	QAISPRTLNAW	Kurane & West, 1999
A*2501 (A25)	p24	71–80	ETINEEAAEW	Klenerman <i>et al.</i> , 1996; van Baalen <i>et al.</i> , 1996
A*2501 (A25)	gp160	703–712	EIIFDIRQAY	Liu <i>et al.</i> , 2006
A*2601 (A26)	p24	35–43	EVIPMFSAL	Goulder <i>et al.</i> , 1996a
A*2601 (A26)	RT	449–457	ETKLGKAGY	Sabbaj <i>et al.</i> , 2003
A29	Nef	120–128	YFPDWQNYT	Draenert <i>et al.</i> , 2004a
A*2902 (A29)	p17	78–86	LYNTVATLY	Masemola <i>et al.</i> , 2004b
A*2902 (A29)	gp160	209–217	SFEPIPIHY	Altfeld, 2000
A30	p17	34–44	LVWASRELERF	Masemola <i>et al.</i> , 2004b
A*3002 (A30)	p17	76–86	RSLYNTVATLY	Goulder <i>et al.</i> , 2001
A*3002 (A30)	RT	173–181	KQNPDIYIY	Goulder <i>et al.</i> , 2001
A*3002 (A30)	RT	263–271	KLNWASQIY	Goulder <i>et al.</i> , 2001
A*3002 (A30)	RT	356–365	RMRGAHTNDV	Sabbaj <i>et al.</i> , 2003
A*3002 (A30)	Integrase	219–227	KIQNFRVYY	Sabbaj <i>et al.</i> , 2003; Rodriguez <i>et al.</i> , 2004
A*3002 (A30)	gp160	310–318	HIGPGRAFY	Sabbaj <i>et al.</i> , 2003
A*3002 (A30)	gp160	704–712	IVNRNRQGY	Goulder <i>et al.</i> , 2001
A*3002 (A30)	gp160	794–802	KYCWNLLQY	Goulder <i>et al.</i> , 2001
A*3101 (A31)	gp160	770–780	RLRDLLLIVTR	Safrit <i>et al.</i> , 1994a,b
A*3201 (A32)	RT	392–401	PIQKETWETW	Harrer <i>et al.</i> , 1996b
A*3201 (A32)	gp160	419–427	RIKQIINMW	Harrer <i>et al.</i> , 1996b

Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
A33	Nef	133–141	TRYPLTFGW	Cao, 2002
A*3303 (A33)	gp160	698–707	VFAVLSIVNR	Hossain <i>et al.</i> , 2001
A*3303 (A33)	gp160	831–838	EVAQRAYR	Hossain <i>et al.</i> , 2001
A*3303 (A33)	Vpu	29–37	EYRKILRQR	Addo <i>et al.</i> , 2002
A66	RT	438–448	ETFYVDGAANR	Rathod, 2006
A*6801 (A68)	Tat	39–49	ITKGLGISYGR	Oxenius <i>et al.</i> , 2002
A*6801 (A68)	Vpr	52–62	DTWAGVEAIR	Sabbaj <i>et al.</i> , 2004
A*6802 (A68)	RT	436–445	GAETFYVDGA	Rathod & Kiepiela, 2005
A*6802 (A68)	Protease	3–11	ITLWQRPLV	Rowland-Jones, 1999
A*6802 (A68)	Protease	30–38	DTVLEEWNL	Rowland-Jones, 1999
A*6802 (A68)	Vpr	48–57	ETYGDTWTGV	Rathod & Kiepiela, 2005
A*6802 (A68)	gp160	777–785	IVTRIVELL	Wilkes, 1999
A*7401 (A19)	Protease	3–11	ITLWQRPLV	Rowland-Jones, 1999
B7	p24	84–92	HPVHAGPIA	Yu <i>et al.</i> , 2002a
B7	RT	156–164	SPAIFQSSM	Linde & Faircloth, 2006
B7	Rev	41–50	RPAEPVPLQL	Yang, 2006
B*0702 (B7)	p24	16–24	SPRTLNAWV	Lewinsohn, 1999
B*0702 (B7)	p24	48–56	TPQDLNTML	Wilson, 1999; Wilkes <i>et al.</i> , 1999; Jin <i>et al.</i> , 2000; Wilson <i>et al.</i> , 1997
B*0702 (B7)	p24	223–231	GPGHKARVL	Goulder, 1999
B*0702 (B7)	Vpr	34–42	FPRIWLHGL	Altfeld <i>et al.</i> , 2001a
B*0702 (B7)	Vif	48–57	HPRVSSEVHI	Altfeld <i>et al.</i> , 2001a
B*0702 (B7)	gp160	298–307	RPNNNTRKSI	Safrit <i>et al.</i> , 1994b
B*0702 (B7)	gp160	843–851	IPRRIRQGL	Wilkes & Ruhl, 1999
B*0702 (B7)	Nef	68–77	FPVTPQVPLR	Haas <i>et al.</i> , 1996; Maier & Autran, 1999
B*0702 (B7)	Nef	68–76	FPVTPQVPL	Bauer <i>et al.</i> , 1997; Frahm & Goulder, 2002
B*0702 (B7)	Nef	71–79	TPQVPLRPM	Goulder, 1999
B*0702 (B7)	Nef	77–85	RPMTYKAAL	Bauer <i>et al.</i> , 1997
B*0702 (B7)	Nef	106–115	RQDILDLWIY	Goulder, 1999
B*0702 (B7)	Nef	128–137	TPGPGVRYPL	Culmann-Penciolelli <i>et al.</i> , 1994; Haas <i>et al.</i> , 1996
B8	gp160	848–856	RQGLERALL	Cao, 2002
B*0801 (B8)	p17	24–32	GGKKKYKLLK	Reid <i>et al.</i> , 1996; Goulder <i>et al.</i> , 1997d
B*0801 (B8)	p17	74–82	ELRSLYNTV	Goulder <i>et al.</i> , 1997d
B*0801 (B8)	p24	128–135	EIYKRWII	Sutton <i>et al.</i> , 1993; Goulder <i>et al.</i> , 1997d
B*0801 (B8)	p24	197–205	DCKTILKAL	Sutton <i>et al.</i> , 1993
B*0801 (B8)	RT	18–26	GPKVKQWPL	Walker <i>et al.</i> , 1989; Sutton <i>et al.</i> , 1993
B*0801 (B8)	gp160	2–10	RVKEYQHL	Sipsas <i>et al.</i> , 1997
B*0801 (B8)	gp160	586–593	YLKDQQLL	Johnson <i>et al.</i> , 1992; Shankar <i>et al.</i> , 1996
B*0801 (B8)	Nef	13–20	WPTVRERM	Goulder <i>et al.</i> , 1997d
B*0801 (B8)	Nef	90–97	FLKEKGGL	Culmann-Penciolelli <i>et al.</i> , 1994; Price <i>et al.</i> , 1997

Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B13	p24	3–11	VQNLQGQMV	Honeyborne <i>et al.</i> , 2007
B13	p24	94–104	GQMREPRGSDI	Honeyborne <i>et al.</i> , 2007
B13	p2p7p1p6	66–74	RQANFLGKI	Honeyborne <i>et al.</i> , 2007
B13	Protease	57–66	RQYDQILIEI	Honeyborne <i>et al.</i> , 2007; Mueller <i>et al.</i> , 2007
B13	RT	333–341	GQGQWYQI	Honeyborne <i>et al.</i> , 2007
B13	Nef	106–114	RQDILDLWI	Harrer <i>et al.</i> , 2005; Honeyborne <i>et al.</i> , 2007
B14	p2p7p1p6	42–50	CRAPRKKGC	Yu <i>et al.</i> , 2002b
B*1401 (B14)	RT	142–149	IRYQYNVL	Rathod, 2006
B*1402 (B14)	p24	166–174	DRFYKTLRA	Harrer <i>et al.</i> , 1996b
B*1402 (B14)	gp160	584–592	ERYLKDQQL	Johnson <i>et al.</i> , 1992
B*1501 (B62)	p24	137–145	GLNKIVRMV	Johnson <i>et al.</i> , 1991; Goulder, 1999
B*1501 (B62)	RT	260–271	LVGKLNWASQIY	Johnson, 1999
B*1501 (B62)	RT	309–318	ILKEPVHGVY	Johnson <i>et al.</i> , 1991; Johnson, 1999
B*1501 (B62)	Nef	117–127	TQGYFPDWQNY	Culmann, 1999
B*1503 (B72)	p24	24–32	VKVIEEKAF	Honeyborne & Kiepiela, 2005
B*1503 (B72)	p24	164–172	YVDRFFKTL	Masemola <i>et al.</i> , 2004b
B*1503 (B72)	Protease	68–76	GKKAIGTVL	Rathod & Bishop, 2006
B*1503 (B72)	RT	496–505	VTDSQYALGI	Sabbaj <i>et al.</i> , 2003
B*1503 (B72)	Integrase	135–143	IQQEFGIPY	Honeyborne & Kiepiela, 2005
B*1503 (B72)	Integrase	185–194	FKRKGGIGGY	Honeyborne, 2003
B*1503 (B72)	Integrase	263–271	RKAKIIRDY	Cao <i>et al.</i> , 2003
B*1503 (B72)	Tat	38–47	FQTKGLGISY	Novitsky <i>et al.</i> , 2001
B*1503 (B72)	Nef	183–191	WRFDSRLAF	Cao, 2002
B*1510 (B71)	p24	12–20	HQAISPRTL	Day, 2005
B*1510 (B71)	p24	61–69	GHQAAMQML	Day, 2003
B*1510 (B71)	Integrase	66–74	THLEGKIIL	Kiepiela <i>et al.</i> , 2007
B*1510 (B71)	Vif	79–87	WHLGHVSI	Honeyborne, 2003
B*1516 (B63)	gp160	375–383	SFNCGGEFF	Wilson <i>et al.</i> , 1997; Wilson, 1999
B18	RT	137–146	NETPGIRYQY	Rathod & Bishop, 2006
B18	RT	175–183	NPEIVYQY	Rathod, 2006
B18	Nef	105–115	RRQDILDWVY	Yang, 2006
B*1801 (B18)	p24	161–170	FRDYVDRFYK	Ogg <i>et al.</i> , 1998
B*1801 (B18)	Vif	102–111	LADQLIHLHY	Altfeld <i>et al.</i> , 2001a
B*1801 (B18)	gp160	31–39	AENLWTVY	Liu <i>et al.</i> , 2006
B*1801 (B18)	gp160	61–69	YETEVHNWV	Liu <i>et al.</i> , 2006
B*1801 (B18)	Nef	135–143	YPLTFGWY	Culmann <i>et al.</i> , 1991; Culmann-Penciolelli <i>et al.</i> , 1994



Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B27	Vpr	31–39	VRHFPRIWL	Addo & Rathod, 2004
B*2703 (B27)	p24	131–140	RRWIQLGLQK	Rowland-Jones <i>et al.</i> , 1998; Rowland-Jones, 1999
B*2705 (B27)	p17	19–27	IRLRPGGKK	McKinney <i>et al.</i> , 1999; Lewinsohn, 1999
B*2705 (B27)	p24	131–140	KRWIILGLNK	Nixon <i>et al.</i> , 1988; Buseyne <i>et al.</i> , 1993; Goulder <i>et al.</i> , 1997c
B*2705 (B27)	gp160	786–795	GRRGWEALKY	Lieberman <i>et al.</i> , 1992; Lieberman, 1999
B*2705 (B27)	Nef	105–114	RRQDILDLWI	Goulder <i>et al.</i> , 1997b
B*3501 (B35)	p17	36–44	WASRELERF	Goulder <i>et al.</i> , 1997a
B*3501 (B35)	p17	124–132	NSSKVSQNY	Rowland-Jones <i>et al.</i> , 1995
B*3501 (B35)	p24	122–130	PPIPVGDIY	Rowland-Jones <i>et al.</i> , 1995
B*3501 (B35)	RT	107–115	TVLDVGDAY	Wilkes & Ruhl, 1999; Wilson <i>et al.</i> , 1999
B*3501 (B35)	RT	118–127	VPLDEDFRKY	Sipsas <i>et al.</i> , 1997; Shiga <i>et al.</i> , 1996
B*3501 (B35)	RT	175–183	HPDIVIYQY	Rowland-Jones <i>et al.</i> , 1995; Shiga <i>et al.</i> , 1996; Sipsas <i>et al.</i> , 1997
B*3501 (B35)	gp160	42–52	VPVWKEATTTL	Wilkes & Ruhl, 1999
B*3501 (B35)	gp160	78–86	DPNPQEVVL	Shiga <i>et al.</i> , 1996
B*3501 (B35)	gp160	606–614	TAVPWNASW	Johnson <i>et al.</i> , 1994
B*3501 (B35)	Nef	74–81	VPLRPMTY	Culmann <i>et al.</i> , 1991; Culmann-Penciolelli <i>et al.</i> , 1994
B*3701 (B37)	Nef	120–128	YFPDWQNYT	Culmann <i>et al.</i> , 1991; Culmann, 1999
B*3801 (B38)	Vif	79–87	WHLGQGVSI	Sabbaj <i>et al.</i> , 2004
B*3801 (B38)	gp160	104–112	MHEDIISLW	Cao, 2002
B*3901 (B39)	p24	61–69	GHQAAMQML	Kurane & West, 1999
B*3910 (B39)	p24	48–56	TPQDLNTML	Honeyborne & Kiepiela, 2005
B*4001 (B60)	p17	92–101	IEIKDTKEAL	Altfeld <i>et al.</i> , 2000
B*4001 (B60)	p24	44–52	SEGATPQDL	Altfeld <i>et al.</i> , 2000
B*4001 (B60)	p2p7p1p6	118–126	KELYPLTSL	Yu <i>et al.</i> , 2002b
B*4001 (B60)	RT	5–12	IETVPVKL	Draenert <i>et al.</i> , 2004b
B*4001 (B60)	RT	202–210	IEELRQHLL	Altfeld <i>et al.</i> , 2000
B*4001 (B60)	gp160	805–814	QELKNSAVSL	Altfeld <i>et al.</i> , 2000
B*4001 (B60)	Nef	37–45	LEKHGAITS	Draenert <i>et al.</i> , 2004b
B*4001 (B60)	Nef	92–100	KEKGGLEGL	Altfeld <i>et al.</i> , 2000
B*4002 (B61)	p17	11–19	GELDRWEKI	Sabbaj <i>et al.</i> , 2003
B*4002 (B61)	p24	70–78	KETINEEAA	Sabbaj <i>et al.</i> , 2003
B*4002 (B61)	p24	78–86	AEWDRVHPV	Sabbaj <i>et al.</i> , 2003
B*4002 (B61)	p2p7p1p6	64–71	TERQANFL	Sabbaj <i>et al.</i> , 2003
B*4002 (B61)	Nef	92–100	KEKGGLEGL	Sabbaj <i>et al.</i> , 2003; Altfeld <i>et al.</i> , 2000

Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B42	Integrase	28–36	LPPIVAKEI	Kiepiela <i>et al.</i> , 2007
B42	Integrase	260–268	VPRRKAKII	Kiepiela & Goulder, 2002
B*4201 (B42)	p24	48–56	TPQDLNTML	Goulder <i>et al.</i> , 2000a
B*4201 (B42)	RT	271–279	YPGIKVRQL	Wilkes & Ruhl, 1999
B*4201 (B42)	Nef	71–79	RPQVPLRPM	Honeyborne, 2006
B*4201 (B42)	Nef	128–137	TPGPGVRYPL	Goulder, 1999
B44	Protease	34–42	EEMNLPGRW	Rodriguez <i>et al.</i> , 2004
B44	gp160	31–39	AENLWVTYV	Borrow <i>et al.</i> , 1997
B*4402 (B44)	p24	162–172	RDYVDRFYKTL	Ogg <i>et al.</i> , 1998
B*4402 (B44)	p24	174–184	AEQASQDVKNW	Lewinsohn, 1999
B*4402 (B44)	gp160	31–40	AENLWVTVYY	Borrow <i>et al.</i> , 1997
B*4403 (B44)	p17	78–86	LYNTVATLY	Masemola <i>et al.</i> , 2004b
B*4415 (B12)	p24	28–36	EEKAFSPEV	Bird <i>et al.</i> , 2002
B*4501 (B45)	p2p7p1p6	1–10	AEAMSQVTNS	Sabbaj <i>et al.</i> , 2004
B50	Nef	37–45	LEKHGAITS	Draenert <i>et al.</i> , 2004b
B51	Vif	57–66	IPLGDAKLII	Bansal <i>et al.</i> , 2004
B51	Vpr	29–37	EAVRHFPRI	Cao <i>et al.</i> , 2003
B*5101 (B51)	RT	42–50	EKEGKISKI	Haas <i>et al.</i> , 1998; Haas, 1999
B*5101 (B51)	RT	128–135	TAFTIPSI	Sipsas <i>et al.</i> , 1997
B*5101 (B51)	gp160	416–424	LPCRKIQII	Tomiyama <i>et al.</i> , 1999
B*5201 (B52)			2 C I V Q	Rammensee <i>et al.</i> , 1999
B*5201 (B52)	p24	143–150	RMYSPTSI	Wilkes & Ruhl, 1999; Wilson <i>et al.</i> , 1997
B53	Nef	135–143	YPLTFGWCF	Kiepiela & Goulder, 2002
B*5301 (B53)	p24	48–56	TPYDINQML	Gotch <i>et al.</i> , 1993
B*5301 (B53)	p24	176–184	QASQEVKNW	Buseyne <i>et al.</i> , 1996, 1997; Buseyne, 1999
B*5301 (B53)	Tat	2–11	EPVDPRLEPW	Addo <i>et al.</i> , 2001
B*5301 (B53)	Nef	135–143	YPLTFGWCY	Sabbaj <i>et al.</i> , 2003
B*5501 (B55)	gp160	42–51	VPVWKEATTT	Shankar <i>et al.</i> , 1996; Lieberman, 1999

Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
B57	p24	32–40	FSPEVIPMF	Frahm <i>et al.</i> , 2005
B57	Protease	70–77	KAIGTVLV	Frahm <i>et al.</i> , 2005
B57	Integrase	123–132	STTVKAACWW	Rodriguez <i>et al.</i> , 2004; Addo & Rathod, 2004
B57	Nef	116–124	HTQGYFPDW	Draenert, 2002
B57	Nef	127–135	YTPGPGIRY	Frahm <i>et al.</i> , 2005
B57	Nef	137–145	LTFGWCFKL	Frahm <i>et al.</i> , 2005
B*5701 (B57)	p24	15–23	ISPRTLNAW	Johnson <i>et al.</i> , 1991; Goulder <i>et al.</i> , 1996b
B*5701 (B57)	p24	30–40	KAFSPEVIPMF	Goulder <i>et al.</i> , 1996b
B*5701 (B57)	p24	108–117	TSTLQEIQGW	Goulder <i>et al.</i> , 1996b
B*5701 (B57)	p24	176–184	QASQEVKNW	Goulder <i>et al.</i> , 1996b
B*5701 (B57)	RT	244–252	IVLPEKDSW	van der Burg <i>et al.</i> , 1997; Hay, 1999
B*5701 (B57)	Integrase	173–181	KTAVQMAVF	Goulder <i>et al.</i> , 1996b; Hay, 1999
B*5701 (B57)	Vpr	30–38	AVRHFPRIW	Altfeld <i>et al.</i> , 2001a
B*5701 (B57)	Vif	31–39	ISKKAKGWF	Altfeld <i>et al.</i> , 2001a
B*5701 (B57)	Rev	14–23	KAVRLIKFLY	Addo <i>et al.</i> , 2001
B*5701 (B57)	Nef	116–125	HTQGYFPDWQ	Culmann <i>et al.</i> , 1991
B*5701 (B57)	Nef	120–128	YFPDWQNYT	Culmann <i>et al.</i> , 1991
B*5703 (B57)	p24	30–37	KAFSPEVI	Goulder <i>et al.</i> , 2000b
B*5703 (B57)	p24	30–40	KAFSPEVIPMF	Goulder <i>et al.</i> , 2000b
B58	p17	76–86	RSLYNTVATLY	Frahm <i>et al.</i> , 2005
B58	Tat	2–11	EPVDPRLPEW	Frahm & Brander, 2005
B58	gp160	59–69	KAYETEVHNVW	Rathod & Bishop, 2006
B*5801 (B58)	p24	108–117	TSTLQEIQGW	Goulder <i>et al.</i> , 1996b; Bertoletti <i>et al.</i> , 1998
B*5801 (B58)	RT	375–383	IAMESIVIW	Kiepiela & Goulder, 2002
B*5801 (B58)	Rev	14–23	KAVRLIKFLY	Addo <i>et al.</i> , 2001
B62	Nef	19–27	RMRAEPAA	Cao, 2002
B63	p17	76–86	RSLYNTVATLY	Frahm <i>et al.</i> , 2005
B63	p24	15–23	ISPRTLNAW	Frahm <i>et al.</i> , 2005
B63	p24	30–40	KAFSPEVIPMF	Frahm <i>et al.</i> , 2005
B63	Rev	14–23	KAVRLIKFLY	Frahm <i>et al.</i> , 2005
B63	Nef	127–135	YTPGPGIRY	Frahm <i>et al.</i> , 2005
B63	Nef	137–145	LTFGWCFKL	Frahm <i>et al.</i> , 2005
B81	Protease	80–90	TPVNIIGRNML	Honeyborne <i>et al.</i> , 2006
B81	RT-Integrase	560–8	LFLDGIDKA	Addo, 2002
B*8101 (B81)	p24	48–56	TPQDLNMTL	Goulder <i>et al.</i> , 2000a
B*8101 (B81)	Vpr	34–42	FPRIWLHGL	Altfeld <i>et al.</i> , 2001a

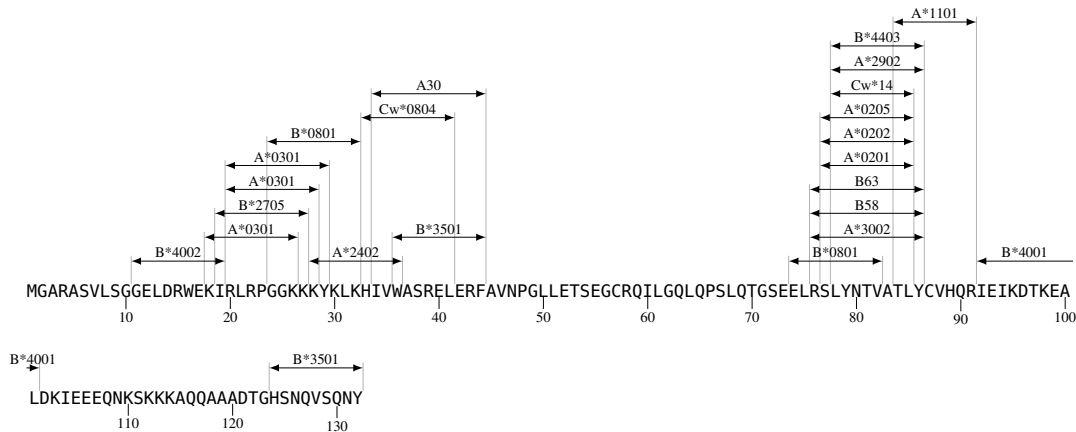
Table I-A.1: Best defined HIV CTL epitopes (cont.).

HLA	Protein	AA	Sequence	Reference
Cw*0102 (Cw1)	p24	36–43	VIPMFSAL	Goulder <i>et al.</i> , 1997a
Cw*0102 (Cw1)	Gag-Pol TF	24–31	NSPTRREL	Liu <i>et al.</i> , 2006
Cw3	Nef	83–91	AALDLSHFL	Draenert <i>et al.</i> , 2004b
Cw*0303 (Cw9)	p24	164–172	YVDRFFKTL	Honeyborne, 2003
Cw*0304 (Cw10)	p24	164–172	YVDRFFKTL	Honeyborne, 2003
Cw*0304 (Cw10)	gp160	557–565	RAIEAQQHL	Currier <i>et al.</i> , 2002; Trocha, 2002
Cw*0401 (Cw4)	gp160	375–383	SFNCGGEFF	Wilson <i>et al.</i> , 1997; Johnson <i>et al.</i> , 1993
Cw5	p24	174–185	AEQASQEVKNWM	Draenert <i>et al.</i> , 2004b
Cw*0501	Rev	67–75	SAEPVPLQL	Addo <i>et al.</i> , 2001
Cw6	Nef	120–128	YFPDWQNYT	Frahm & Brander, 2005
Cw7	Nef	105–115	KRQEILDLWVY	Kiepiela & Goulder, 2002; Yu <i>et al.</i> , 2002a
Cw8	gp160	557–565	RAIEAQQHM	Bishop & Honeyborne, 2006
Cw8	Nef	82–91	KAAVDLSHFL	Harrer <i>et al.</i> , 1996b
Cw*0802 (Cw8)	p24	48–56	TPQDLNTML	Goulder <i>et al.</i> , 2000a; Honeyborne & Kiepiela, 2005
Cw*0802 (Cw8)	RT	495–503	IVTDSQYAL	Rathod & Honeyborne, 2006
Cw*0802 (Cw8)	Nef	83–91	AAVDLSHFL	Cao <i>et al.</i> , 2003; Rathod & Honeyborne, 2006
Cw*0804 (Cw8)	p17	33–41	HLVWASREL	Masemola <i>et al.</i> , 2004b
Cw12	Tat	30–37	CCFHCQVC	Cao <i>et al.</i> , 2003; Nixon <i>et al.</i> , 1999
Cw14	p17	78–85	LYNTVATL	Horton & Havenar-Daughton, 2005
Cw15	gp160	557–565	RAIEAQQHL	Trocha, 2002
Cw18	p24	142–150	VRMYSVSI	Honeyborne, 2006
Cw18	p24	161–169	FRDYVDRFF	Honeyborne & Kiepiela, 2005
Cw18	Integrase	165–172	VRDQAEHL	Rathod & Honeyborne, 2006
Cw18	gp160	511–519	YRLGVGALI	Honeyborne, 2006

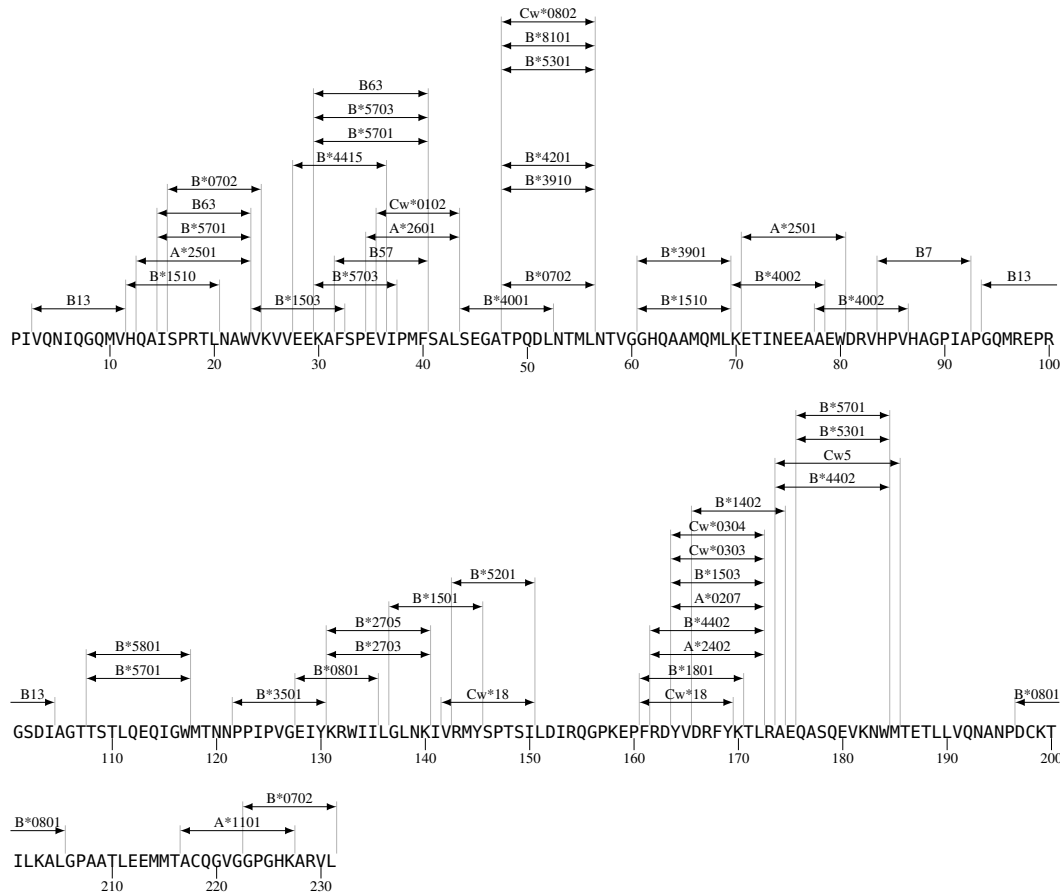
### I-A-6 Map of optimal HIV-1 CTL epitopes

The location and HLA restriction elements of CTL epitopes are indicated on protein sequences of HXB2. These maps are meant to provide the relative location of defined epitopes on a given protein, but the HXB2 sequence may not actually carry the epitope of interest, as it may vary relative to the sequence for which the epitope was defined.

#### p17 Optimal CTL Epitope Map



#### p24 Optimal CTL Epitope Map

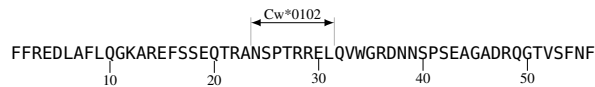


Reviews

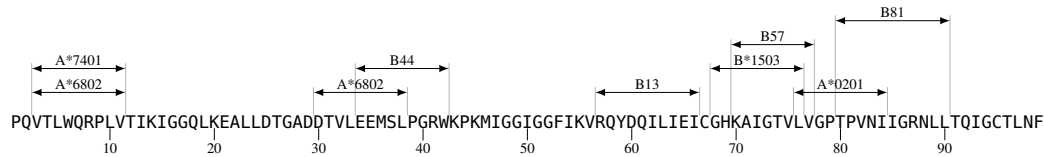
p2p7p1p6 Optimal CTL Epitope Map



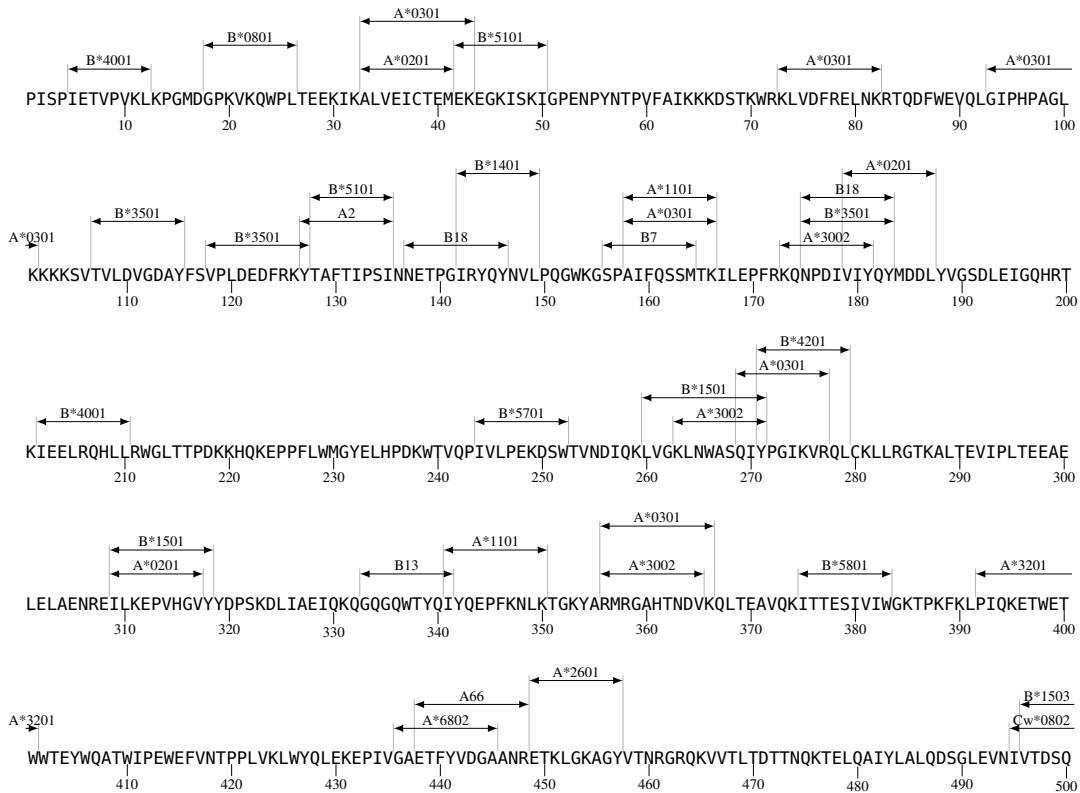
Gag/Pol TF Optimal CTL Epitope Map

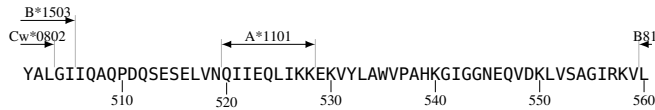


Protease Optimal CTL Epitope Map

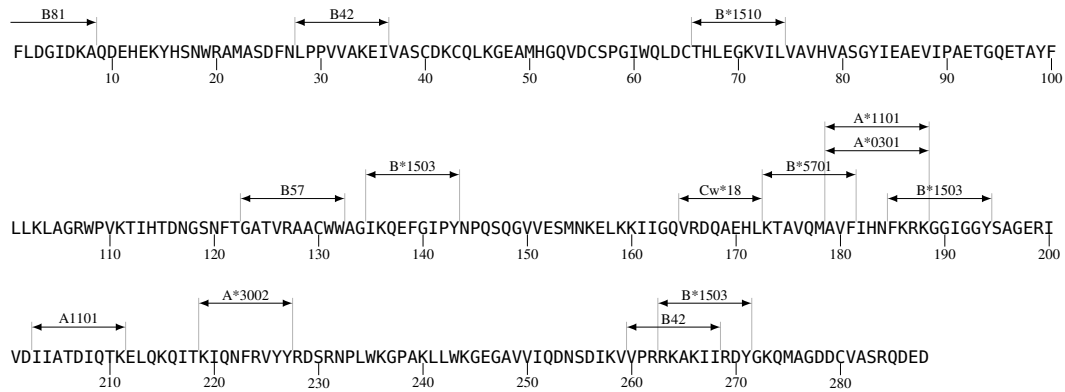


RT Optimal CTL Epitope Map

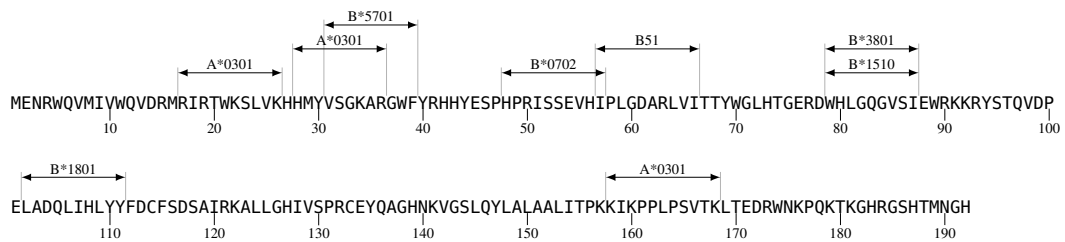




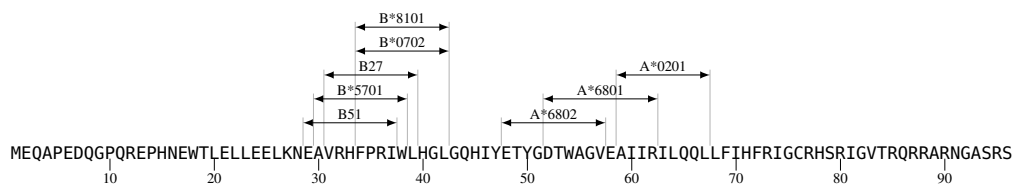
Integrase Optimal CTL Epitope Map



Vif Optimal CTL Epitope Map



Vpr Optimal CTL Epitope Map

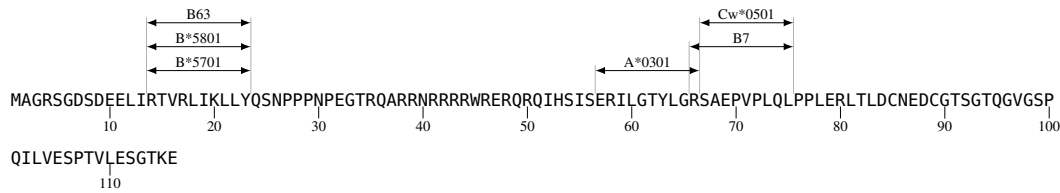


Tat Optimal CTL Epitope Map

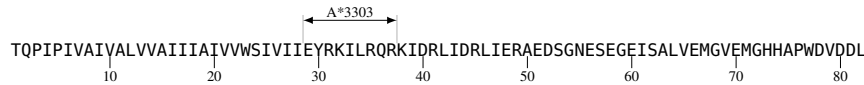


Reviews

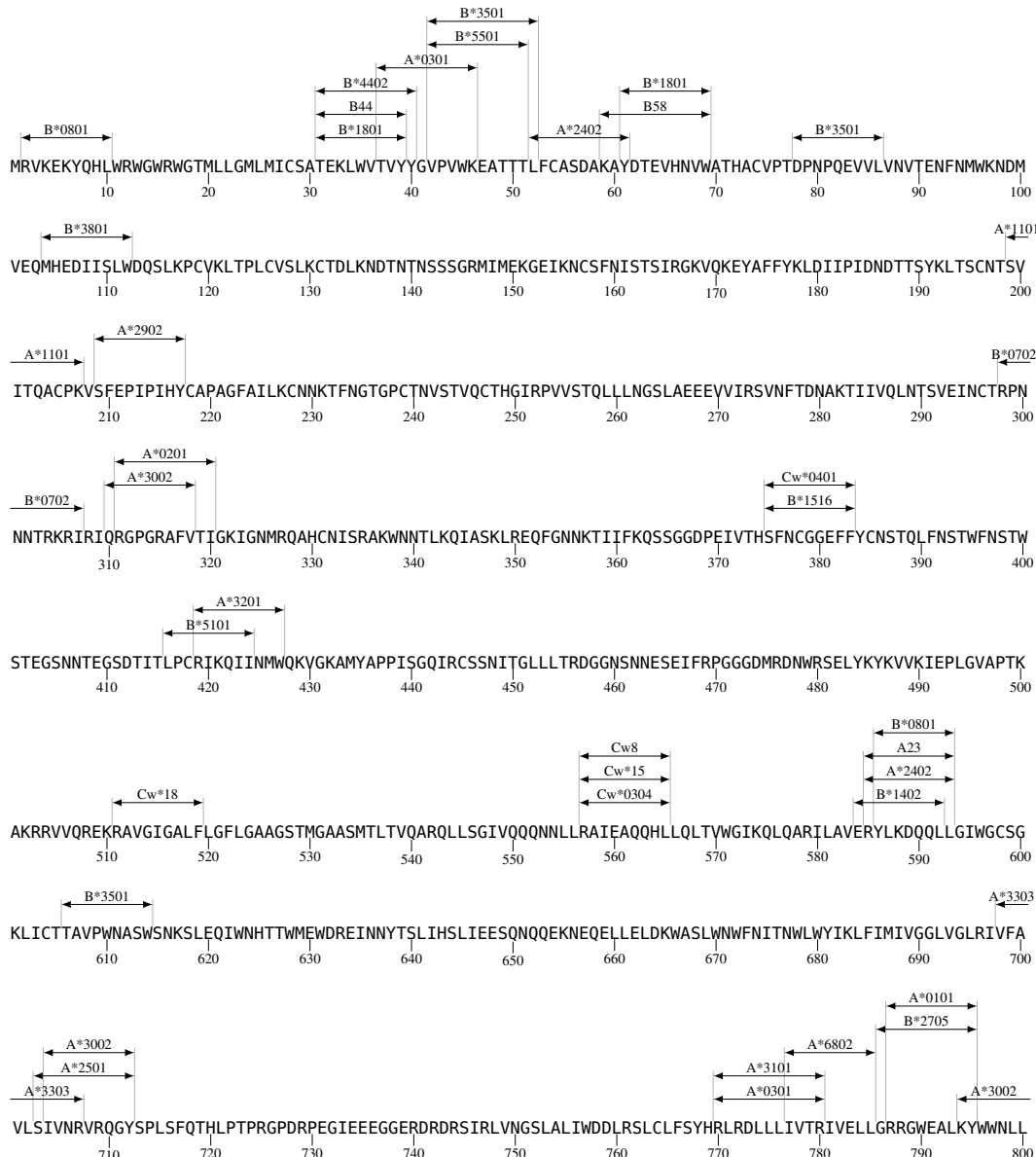
Rev Optimal CTL Epitope Map



Vpu Optimal CTL Epitope Map



gp160 Optimal CTL Epitope Map



Reviews

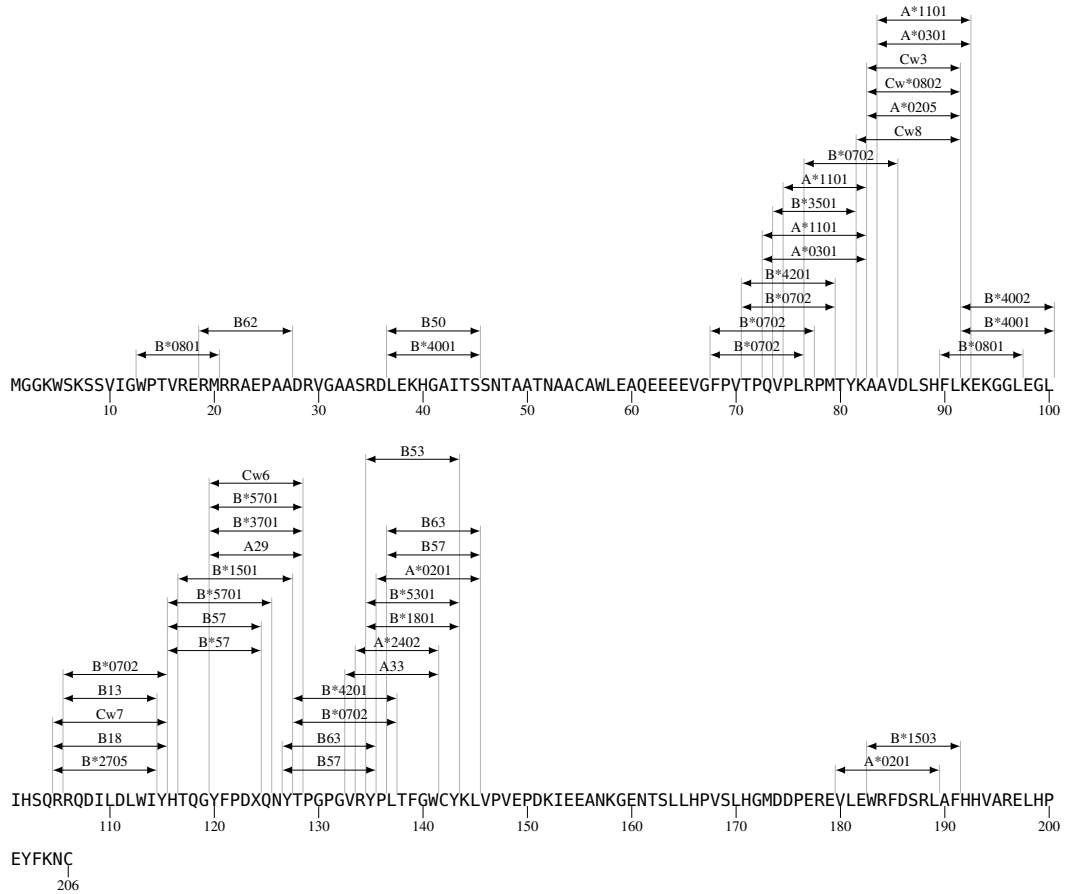


## Map of optimal HIV-1 CTL epitopes

## Optimal HIV-1 CTL Epitopes



## Nef Optimal CTL Epitope Map



## I-A-7 Acknowledgments

We would like to express our gratitude to the large number of researchers in the field who continuously contribute to this database. We very much welcome any criticism, comments and additions to this list since we are sure that some epitopes will unintentionally escape our attention, despite close monitoring of the literature. Also, we would like to especially invite suggestions as to the use of alternative or additional selection criteria to define optimal epitopes as we strive to make this listing as extensive and useful to the community as possible, while maintaining its integrity. Please write or call us with any comments you may have at:

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**Part II**

# **HIV CTL/CD8 + Epitopes**

CTL CD8+



## II-A

# Summary

This part includes tables, maps, and associated references of HIV-specific CTL epitopes found in the literature arranged sequentially according to the location of the proteins in the HIV-1 genome. We attempted to make this part as comprehensive as possible, requiring that the epitope be contained within a defined region of a maximum of 30 amino acids, but not that the optimal boundaries be defined. Studies that were based on the analysis of whole proteins are described at the end of each protein section. The same epitope can have multiple entries, as each entry represents a single publication in this part of the database. For more recent updates, epitope sequence alignments, and useful search capabilities, please see our web site: <http://www.hiv.lanl.gov/content/immunology>. For a concise listing of only the best defined CTL epitopes, see the summary by Nicole Frahm, Brett Baker and Christian Brander on page 3 in Part I of this compendium. CTL responses to proteins with no defined epitopes are listed at the end of each protein section.

Recent studies utilize multiple functions attributed to T cells to define responses, and the simple distinctions of cytotoxic T-cell and helper T-cells have become blurred as more is learned about the range of responses triggered in CD4 and CD8 positive T-cells responding to antigenic stimulus. When adding the most recent studies to the database, we have tried to place T cell responses in a reasonable manner into our traditional helper T cell and CTL parts, and to specify the assay used to measure the response in each study.

### II-A-1 Epitope tables

Each CTL reference has a multi-part basic entry:

**HXB2 location:** The viral strain HXB2 (GenBank Accession Number K03455) is used as a reference strain throughout this publication. The position of the defined epitope location relative to the sequence of the HXB2 protein is indicated. The numbering in this table corresponds to the protein maps. Because of HIV-1 variation the epitope may not actually be present in HXB2; rather, the position in HXB2 indicates the position aligned to the epitope. HXB2 was selected as the reference strain because so many studies use HXB2, and because crystal structures for HXB2-related proteins are often available. The precise positions of an

epitope on the HXB2 reference strain can be readily obtained using the interactive position locator at our web site: <http://www.hiv.lanl.gov/content/sequence/LOCATE/locate.html>.

**Author location:** The amino acid positions of the epitope boundaries and the reference sequence are listed as given in the primary publication. Frequently, these positions as published are imprecise, and do not truly correspond to the numbering of the sequence, but they provide a reasonable guide to the peptide's approximate location in the protein. Also, in many cases the reference sequence identification was not provided, and in such cases it is not possible to use these numbers to specify precise locations.

**Epitope:** The amino acid sequence of the epitope of interest as defined in the reference, based on the reference strain used in the study defining the epitope. On occasions when only the position numbers and not the actual peptide sequence were specified in the original publication, we tried to fill in the peptide sequence based on the position numbers and reference strain. If the sequences were numbered inaccurately by the primary authors, or if we made a mistake in this process, we may have misrepresented the binding site's amino acid sequence. Because of this uncertainty, epitopes that were not explicitly written in the primary publication, that we determined by looking up the reference strain and the numbered location, are followed by a question mark in the table.

**Epitope name:** If the epitope has a name attributed by the publication, it is recorded here, e.g. "SL9".

**Subtype:** The subtype under study, if specified in the primary publication; this is generally not specified for B subtype.

**Immunogen:** The antigenic stimulus of the CTL response. Often this is an HIV-1 infection. If a vaccine was used as the original antigenic stimulation, not a natural infection, this is noted, and additional information about the vaccine antigen is provided as available.

**Species (MHC):** The species responding and MHC or HLA specificity of the epitope.

**Donor MHC:** The HLA genotype of the individual that responded to the epitope.

**Country:** The country where the samples were obtained; this is generally not specified if the study was conducted in the United States.

**Assay type:** Assays used to characterize the response.

**Keywords:** Keywords are a searchable field for the web interface that is included in the T-cell sections of the printed version to help identify entries of particular interest.

**Reference:** The primary reference (sometimes two or more directly related studies are included). Details for some of the earlier references are in Part V.

Following the entry for a given CTL epitope brief comments explain the context in which the epitope was studied and what was learned about the epitope in a given study.

## II-A-2 HIV protein epitope maps

All HIV CTL epitopes mapped to within a region of 14 amino acids or less are indicated on the HIV protein epitope maps. The location and HLA restriction elements of CTL epitopes are indicated on protein sequences of HXB2. These maps are meant to provide the relative location of defined epitopes on a given protein, but the HXB2 sequence may not actually carry the epitope of interest, as it may vary relative to the sequence for which the epitope was defined. Epitopes with identical boundaries and HLA fields are included in the maps only once. If one laboratory determines HLA presenting molecules at the serotype level (example: A2) and another at the genotype level (example: A\*0201) both will be included in the map. MHC specificities are indicative of the host species; when no MHC presenting molecule is defined, the host species is noted.

## II-A-3 Alignments

To conserve space, no epitope alignments are provided in this book, but they can be generated using the CTL epitope search tool at <http://www.hiv.lanl.gov/content/immunology>. The master protein sequence alignment files from which the epitope alignments were created are available at our web site at <http://www.hiv.lanl.gov/content/sequence/NEWALIGN/align.html>.

## II-B

# HIV CTL/CD8+ Epitope Tables

All HIV CTL epitopes are arranged by protein position. The table entries are sorted in a nested way—first by protein, then by HXB2 start location, and finally by HLA presenting molecule. CTL reactions against proteins with undefined epitopes are listed at the end of the protein that stimulated the response.

### II-B-1 Gag p17 CTL/CD8+ epitopes

**HXB2 Location** p17 (1–10)  
**Author Location** Gag  
**Epitope** MGARASVLSG  
**Subtype** CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11.1)  
**Country** Thailand  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** optimal epitope  
**References** Kantakamalakul *et al.* 2006

- T cell responses in CRF01\_AE infected individuals from Thailand were studied.
- This single peptide elicited IFN-gamma responses from three subjects and may be an A\*1101 binding peptide.

**HXB2 Location** p17 (5–13)  
**Author Location** Gag (5–13 SUMA)  
**Epitope** ASVLSGGEL  
**Epitope name** Gag AL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells  
**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.

- The patient SUMA maintained low viral loads and stable CD4 T-cell counts through 7 years of followup. In contrast to more rapid progressors WEAU and BORI, SUMA had a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only 4 epitopes acquired escape mutations in SUMA over time, and this was 1 of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** p17 (5–15)  
**Author Location** Gag (5–15)  
**Epitope** ASILRGGKLDK  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p17 (5–19)  
**Author Location** p17 (5–19)  
**Epitope** ASVLSGGELDRWEKI  
**Epitope name** AI14  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** binding affinity, subtype comparisons, acute/early infection  
**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants

are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.

- This peptide, ASVLSGGELDRWEKI contains the CON clade-B putative epitope AI14. No cross-recognition of variants was seen across clades or intra-clade central sequences. Variant ASVLSGGkLdaWEKI was seen in clade A and M-group; variant ASiLrGGkLdkWEKI in clade C; ASVLSG-GkLdkWEKI in clade-B ANC; and variant ASVLSGGELDKWEKI in clade-B COT.

**HXB2 Location** p17 (6–15)

**Author Location** Gag (Henan isolate)

**Epitope** SVLSGGQLDR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (8–18)

**Author Location** Gag (8–18)

**Epitope** LSGGELDRWEK

**Epitope name** Gag 1.2

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade  
*HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu

**Species (MHC)** macaque

**Assay type** T-cell Elispot, Intracellular cytokine staining

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization, memory cells

**References** Amara *et al.* 2005

- A clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better conserved for CD8 than CD4 T cells.
- All 5 CD8 and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. The similar reported human epitope in this case is GELDRWEKI. HLA restriction: B\*4002, B62
- Conservation across other clades: none. The form that is most common in CRF02, LSGGkLdaWEK, does not cross-react with the B clade elicited response.

**HXB2 Location** p17 (11–19)

**Author Location**

**Epitope** GELDRWEKI

**Epitope name** Gag-GI9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4002)

**Donor MHC** 01RCH46: A\*0201, A\*0217, B\*0801, B\*4002, Cw\*0303, Cw\*0701

**Keywords** HAART, ART

**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 01RCH46 was Hispanic, on HAART, and had a viral load of 21000 and CD4 count of 623 – she also recognized KETINEEAA p24(70-78), HLA B\*4002, and TAFTIPSI, RT(128-135), HLA A\*0217.
- Among HIV+ individuals who carried HLA B40, 2/5 (40%) recognized this epitope.

**HXB2 Location** p17 (11–19)

**Author Location** p17 (11–19)

**Epitope** GELDRWEKI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4002)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** p17 (11–19)

**Author Location** p17 (11–19)

**Epitope** GELDRWEKI

**Epitope name** GI9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B40)

**Donor MHC** A\*30, B\*18, B\*40, Cw\*02, Cw\*05

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion

**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.

- The escape variant geldrwKki was detected in 10/10 maternal clones from a B40-positive mother, but was absent in all sequences from her B40-negative infant, sampled at months 2, 4, and 11, suggesting either transmission of a minority wild-type variant, or rapid reversion in the absence of continued CTL pressure.
- geldrwKki elicited lower responder cell frequencies than GELDRWEKI.

**HXB2 Location** p17 (11–19)

**Author Location** p15

**Epitope** GELDRWEKI

**Epitope name** B40-GI9(p15)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B40)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p17 (11–30)

**Author Location** Gag (11–30)

**Epitope** GELDRWEKIRLRPGGKKKYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Donor MHC** A2, A32, B27, B62

**Assay type** Chromium-release assay

**Keywords** genital and mucosal immunity

**References** Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCR $\beta$  VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood and semen.

**HXB2 Location** p17 (12–21)

**Author Location** p17

**Epitope** ELDRWEKIRL

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B63)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA B63 epitope containing the B58 super-type binding motif embedded in a reactive peptide. There is no evidence for B57/B58 cross-presentation of this epitope.

**HXB2 Location** p17 (16–30)

**Author Location** p17 (16–30 HXB2)

**Epitope** WEKIRLRPGGKKKYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p17 (17–34)

**Author Location** p17

**Epitope** EKIRLRPGGKKKYKIKHI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but

the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.

- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. *J. Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, EKIRLRPGGKKKYKCLKHI, had an overall frequency of recognition of 16.7% - 22% AA, 15.4% C, 15.9% H, 4.8% WI.

**HXB2 Location** p17 (18–26)  
**Author Location** p17 (18–26 IIIB)  
**Epitope** KIRLRPGGK  
**Immunogen**  
**Species (MHC)** human (A\*0301)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes that this is an A\*0301 epitope.

**HXB2 Location** p17 (18–26)  
**Author Location**  
**Epitope** KIRLRPGGK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**Keywords** acute/early infection  
**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWILGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.

- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWV, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** p17 (18–26)  
**Author Location** p17 (18–26 SF2)  
**Epitope** KIRLRPGGK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**References** Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- The reactive peptide p17 gag WEKIRLRPGGKKKYK contained two A\*0301-restricted epitopes, KIRLRPGGK and RLRPGGKKK A\*0301.

**HXB2 Location** p17 (18–26)  
**Author Location** p17 (18–26)  
**Epitope** KIRLRPGGK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B  
**Keywords** Th1, characterizing CD8+ T cells  
**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8+ cells are found, each one constituting 30-40% of the CD8+ cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Two of seven patients responded to this peptide with GzB producing cells, while none of the patients responded with IFN-gamma producing cells.

**HXB2 Location** p17 (18–26)  
**Author Location** p17  
**Epitope** KIRLRPGGK  
**Subtype** A  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**Donor MHC** A\*0101, A\*0301, B\*0801; A\*0201, A\*3101, B\*3501, B\*3905  
**Country** United Kingdom  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** escape, acute/early infection, variant cross-recognition or cross-neutralization  
**References** Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. CTL escape variants were often transmitted. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those



epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient.

- A\*0301 epitopes RLRPGGKKK and KIRLRPGGK, and B\*0801 epitope GGKKKYRL, overlap. In 1 donor, the transmitted virus carried the escape form for 2 of these epitopes. The double substitution kirlrpggR results in escape from response in the donor. Similarly, the double substitution ggRkkyKl results in escape for this epitope.
- The escape mutation kirlrpggR in this epitope resulted in 74% reduction in HLA binding affinity. The other variant tested, kirlrQggR, resulted in 90% reduction.

**HXB2 Location** p17 (18–26)

**Author Location** p17

**Epitope** KIRLRPGGK

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (A03)

**Assay type** Tetramer binding

**Keywords** binding affinity

**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, KIRLRPGGK (MHC Class I restriction, serotype Bw6) complexed with MHC A03 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–28 B1 and B2)

**Epitope** KIRLRPGGK

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A03, A32, B08, B62, Cw3)

**Country** Netherlands

**Assay type** Other

**Keywords** subtype comparisons, computational epitope prediction, superinfection

**References** Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01\_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-A03 restricted epitope, KIRLRPGGK, is the dominant gag epitope in Caucasians and varied to KIRLRPGGr, KIRLRPGGs or KIRLRPGGK. Mutant KIRLRPGkK was found at 42% in strain B1 after 4 years while mutant KIRLRPGGs was found in 100% of B2 after 3 years. Though the

infecting variant in CRF01\_AE was KIRLRPGGq, no changes were seen in it with time.

**HXB2 Location** p17 (18–26)

**Author Location** Gag (Henan isolate)

**Epitope** KIRLRPGGK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26 IIIB)

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- KIRLRPGGR and RIRLRPGGR, naturally occurring variants, were found in mother and are escape mutants.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26)

**Epitope** KIRLRPGGK

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A3)

**Keywords** dendritic cells

**References** Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYK-TLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

**HXB2 Location** p17 (18–26)

**Author Location** Gag (18–26)

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Brodie *et al.* 1999

- The ability of CTL effector cells was studied by expanding autologous HIV-1 Gag-specific CTL *in vitro*, and adoptive transfer.
- The transferred CTLs migrated to the lymph nodes and transiently reduced circulating productively-infected CD4+ T cells, showing that CTL move to appropriate target sites and mediate anti-viral effects.

**HXB2 Location** p17 (18–26)

**Author Location** (18–26)

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Brodie *et al.* 2000

- Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL.
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication.
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1alpha and MIP-1beta, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism.
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26 IIIB)

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** transgenic mouse (A3)

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- KIRLRPGGR and RIRLRPGGR were escape mutants.
- This epitope was recognized and many escape mutants were detected in an HLA A3 transmitting mother, and was recognized but invariant in an HLA A3 non-transmitting mother.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26 IIIB)

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** review, escape

**References** Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical sibling hemophiliac brothers were both infected with the same batch of factor VIII. Goulder *et al.* [1997e] is a review of immune escape that summarizes this study.

- One had a response to this epitope, the other did not. They were tested 6-8 years after infection.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (subtype B)

**Epitope** KIRLRPGGK

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A3)

**References** Kaul *et al.* 2000

- 11 of 16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8+ gamma-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T-cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (SF2)

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- WEKIRLRPGGKKKYKCLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – 7/10 that had a dominant response to this epitope were A3, and 5/7 targeted RLRPGGKKK while 2/7 targeted KIRLRPGGK.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNMLNTVVG (p24 41-60), and WEKIRLRPGGKKKYKCLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNMLNTVVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p17 (18–26)

**Author Location** p17

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** HAART, ART

**References** Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26 SF2)

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 3/7 group 1, 0/4 group 2, and 2/2 group 3.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26)

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A3)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- KIRLRPGGK is cross-reactive for A, B, and D clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (JRCSF)

**Epitope** KIRLRPGGK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Severino *et al.* 2000

- Primary HLA-A3+ CD4+ and HLA-mismatched lymphocytes from uninfected donors were infected with JRCSF after isolation then cocultured with the A3-restricted CTL clone 11504/A7 specific for KIRLRPGGK, and viral inhibition was MHC-restricted.
- Primary monocytes and monocyte-derived DC were generated from the same donors, replication of HIV-1 in these cell types was less efficient than in lymphocytes and could also be inhibited by MHC-restricted CTL.
- DC-lymphocyte cluster cultures allowed vigorous viral replication and MHC-restricted CTL viral inhibition was blunted or lost depending on the ratio of DC to CD4+ lymphocyte in the culture.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26)

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP).
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

**HXB2 Location** p17 (18–26)

**Author Location** p17

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** dendritic cells

**References** Ostrowski *et al.* 2000

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*.
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T cell help in 9 of 10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T cell help to a variable degree in most of patients.
- Those CTL that didn't respond to CD40LT could expand with IL2 present, and IL15 produced by dendritic cells also contributes.
- The T-helper epitope used for CD4+ T-cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKAN-SKFIGITE)

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26)

**Epitope** KIRLRPGGK

**Epitope name** A3-KK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), immunodominance, acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.

- 8/14 HLA-A3 positive individuals had detectable A3-restricted responses during acute infection. Only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 7/8 individuals with acute responses had specific responses for this epitope.
- KIRLRPGGK and RLRPGGKKK were the most commonly recognized HLA-A3 epitopes during acute infection, after 1 year of treatment, and after STI. RLRPGGKKK was immunodominant.

**HXB2 Location** p17 (18–26)  
**Author Location** p17 (18–26)  
**Epitope** KIRLRPGGK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, escape  
**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** p17 (18–26)  
**Author Location** p17 (18–26 B consensus)  
**Epitope** KIRLRPGGK  
**Epitope name** KK9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** epitope processing, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2004

- KK9 and RK9 overlap, are presented by HLA-A3, and are frequently immunodominant and involved in acute-phase primary responses. A mutation in the C-terminal flanking residue of KK9 (K to Q) (kirlrpkkq-Q) inhibits processing of the immunodominant gag KK9 epitope, resulting in rapid decline in the KK9 specific CD8+ T-cell response. At the same time it abrogates the response to RK9 through the embedded mutation rlrpggkQk. Transmission of this mutation to patients expressing HLA-A3 prevents acute-phase response to these epitopes, although the mutation can eventually revert to wild-type allowing a delayed response to the epitope.

**HXB2 Location** p17 (18–26)  
**Author Location** p17  
**Epitope** KIRLRPGGK  
**Epitope name** KK9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Keywords** review, epitope processing, escape  
**References** Goulder & Watkins 2004

- This paper is a review of the role of CTL in HIV infection, and it uses KK9 as an example of an epitope that escapes due to a mutation beyond the epitope on the C-terminal side that probably affects proteasomal processing.

**HXB2 Location** p17 (18–26)  
**Author Location** (B consensus)  
**Epitope** KIRLRPGGK  
**Epitope name** KK9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A03, B14, B60, Cw3, Cw7  
**Country** United States  
**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells  
**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- One of nine individuals recognized this epitope.

**HXB2 Location** p17 (18–26)  
**Author Location** p17  
**Epitope** KIRLRPGGK  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (A3)  
**Donor MHC** A01, A03, B39, B44, Cw4, Cw6  
**Assay type** T-cell Elispot  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 3/11 HIV epitopes tested in an IFN-gamma EliSpot assay. Responses were detected 16 and 20 weeks after exposure, but were lost by week 80.

**HXB2 Location** p17 (18–26)

**Author Location** Gag (18–26)

**Epitope** KIRLRPGGK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** p17 (18–26)

**Author Location** p24

**Epitope** KIRLRPGGK

**Epitope name** KK9

**Immunogen**

**Species (MHC)** (A3)

**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion

**References** Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26)

**Epitope** KIRLRPGGK

**Epitope name** KR9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A\*03, A\*31, B\*08, B\*15, Cw\*04, Cw\*07

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion

**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.

- The escape variant kirlrpggR was present in 10/10 clones from an A3+ mother, was transmitted to her infant, and present in 10/10 clones at months 2 and 4, but decreased to 0/10 clones by 15 months of age in her A3- child.

**HXB2 Location** p17 (18–26)

**Author Location** p17

**Epitope** KIRLRPGGK

**Epitope name** A3-KK9(p17)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26)

**Epitope** KIRLRPGGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301, A3, B27)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p17 (18–26)

**Author Location** p17 (18–26)

**Epitope** KIRLRPGGK

**Epitope name** A3-KK9 Gag

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** epitope processing, supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response. This epitope did not vary, although the response declined over time. The authors suggest

this might be due to a downstream Arg -> Thr substitution at C+2 that may impair processing.

**HXB2 Location** p17 (18–26)  
**Author Location** p17 (18–26)  
**Epitope** KIRLRPGGKK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*0101, A\*0301, B\*0801; A\*0201, A\*3101, B\*3501, B\*3905  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** HAART, ART, escape, viral fitness and reversion  
**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate escape rate for this epitope, KIRLRPGGKK, was 0.002 (SE 0.006), and best estimate reversion rate was 0/day with a SE of 0.
- The variant K26R confers escape in A\*0301+ individuals. On transmission to an HLA A\*0301-negative recipient, the mutation did not revert to wild type over a period of 1 year.

**HXB2 Location** p17 (18–27)  
**Author Location** (C consensus)  
**Epitope** KIRLRPGGKK  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p17 (18–27)  
**Author Location** Gag  
**Epitope** KIRLRPGGKK  
**Epitope name** 1272  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA  
**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KIRLRPGGKK: 36%. This epitope has been previously reported to be presented by A3, B27, B62, Bw62 and is an A11 binder, but was not confirmed as a CTL target in this study.

**HXB2 Location** p17 (18–27)  
**Author Location** Gag (Henan isolate)  
**Epitope** KIRLRPGGKK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (18–27)  
**Author Location** p17 (18–27)  
**Epitope** KIRLRPGGKK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)

**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong T-helper cell responses. Only patients starting with moderately high viral load (VL) were able

to reduce the VL set point. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up.

- 8/14 patients recognized this epitope.

**HXB2 Location** p17 (18–27)

**Author Location** p17 (18–27 LAI)

**Epitope** KIRLRPGGKK

**Subtype** B

**Immunogen**

**Species (MHC)** human (B27)

**References** Brander & Walker 1996

- D. Lewinsohn, pers. comm.

**HXB2 Location** p17 (18–27)

**Author Location** p17 (18–27)

**Epitope** KIRLRPGGKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

**HXB2 Location** p17 (18–27)

**Author Location** Gag

**Epitope** KIRLRPGGKK

**Epitope name** KK10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Assay type** Other

**Keywords** rate of progression, escape

**References** Gao *et al.* 2005

- Three distinct HLA alleles known to alter the rate of AIDS progression were studied. B\*57-mediated protection occurs early in infection and the protective effect of this allele subsides after CD4 cell count drops. In contrast, B\*27 shows no protection against progression to CD4<200, but rather delays progression to an AIDS-defining illness after the CD4 counts have dropped. B\*35-mediated rapid progression to AIDS is probably a function of early decline in CD4 counts.
- KK10 escape occurs late and was shown to precede a sharp increase in viral load. The authors hypothesize the B27 benefit may arise due to enduring HLA restriction after escape from many other allotype responses has occurred.

**HXB2 Location** p17 (18–31)

**Author Location** p17 (18–31)

**Epitope** KIRLRPGGKKKYKL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

**HXB2 Location** p17 (18–31)

**Author Location** p17 (18–31)

**Epitope** KIRLRPGGKKKYKL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**References** Lubaki *et al.* 1997

- 82 HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of CTL response.
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response.
- A subject who was HLA-B62+ had CTL that recognized this peptide, and p24 LGLNKIVRMYS, and one additional unknown epitope.

**HXB2 Location** p17 (18–32)

**Author Location** Gag (17–31)

**Epitope** KIRLRPGGKKKYKLLK

**Epitope name** KK15

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- One subject responded to peptide KK15 which had a K26R mutation, KIRLRPGGKrKYKLLK, in a minority of plasma virus clones.

**HXB2 Location** p17 (18–42)

**Author Location** p17 (18–42 IIIB)

**Epitope** KIRLRPGGKKKYKLLKHIVWASRELE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Jassoy *et al.* 1992

- Epitope recognized by CTL clone derived from CSF.

**HXB2 Location** p17 (18–42)

**Author Location** p17 (18–42 PV22)

**Epitope** KIRLRPGGKKKYKLLKHIVWASRELE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Jassoy *et al.* 1993

- HIV-1 specific CTLs release  $\gamma$ -IFN, and  $\alpha$ - and  $\beta$ -TNF.

**HXB2 Location** p17 (18–42)

**Author Location** p17 (18–42 BH10)

**Epitope** KIRLRPGGKKKYKLLKHIVWASRELE

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**References** Johnson *et al.* 1991

- Gag CTL response was studied in three individuals.

**HXB2 Location** p17 (19–27)

**Author Location** p17 (19–27 JRCFSF)

**Epitope** IRLRPGGKK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*2705)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008  
 • Noted by Brander to be B\*2705.

**HXB2 Location** p17 (19–27)  
**Author Location** p17 (19–27 LAI)  
**Epitope** IRLRPGGKK  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (B27)  
**References** Brander & Walker 1996

**HXB2 Location** p17 (19–27)  
**Author Location** p17 (19–27 JRCSF)  
**Epitope** IRLRPGGKK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** scid-hu mouse (B27)  
**Keywords** escape  
**References** McKinney *et al.* 1999

- Epitope-specific CTL were infused in infected human PBL-SCID mice, and transient decreases in viral load were observed, however virus was not eradicated and the HIV-specific CTL rapidly disappeared.
- No escape mutants were observed.
- Control CTL were long lived in both infected and uninfected mice, showing the rapid loss of CTL was due to target interaction.

**HXB2 Location** p17 (19–27)  
**Author Location** p17 (SF2)  
**Epitope** IRLRPGGKK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Keywords** subtype comparisons, immunodominance  
**References** Goulder *et al.* 2000a

- WEKIRLRPGGKKKYKLLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – 2/3 individuals that were B27+ had a dominant response to this epitope.
- Three peptides GSEELRSLYNTVATL (p17 residues 71–85), SALSEGATPQDLNLTMLNTVG (p24 41–60), and WEKIRLRPGGKKKYKLLK (p17 16–30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20–36), ELRSLYNTVATLYCV (p17Gag 74–88), SALSEGATPQDLNLTMLNTVG (p24 41–60), FRDYVDRFFKTLRAEQA (p24 161–177), and SILDIKQGKEPFRDY (p24 149–164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p17 (19–27)  
**Author Location** p17 (19–27)  
**Epitope** IRLRPGGKK  
**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)  
**References** Day *et al.* 2001

**HXB2 Location** p17 (19–27)  
**Author Location** p17 (19–27)  
**Epitope** IRLRPGGKK  
**Epitope name** IK9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Keywords** immunodominance, escape  
**References** Goulder *et al.* 2001b

- This B27 epitope is generally recognized only if there is escape in the B27 dominant epitope, p24 KRWILGLNK.

**HXB2 Location** p17 (19–27)  
**Author Location** Gag  
**Epitope** IRLRPGGKK

**Epitope name** IK9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Donor MHC** A26, B27  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** responses in children, rate of progression, immunodominance, escape  
**References** Feeney *et al.* 2004

- Viral load in a perinatally infected child remained low until emergence of an escape variant (kTwiilglnk) in the immunodominant CTL epitope KRWILGLNK when the child was 7.4 years old. The emergence of this escape mutation was followed by an increase in viremia and an increase in the number of targeted CTL epitopes, measured again when the child was 9.2 years old. A low level response to IK9 was the only other epitope recognized prior to the loss of immune control and broadening of the response, and was detected in the 7.4 year sample.

**HXB2 Location** p17 (19–27)  
**Author Location** p17 (19–27)  
**Epitope** IRLRPGGKK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Donor MHC** A1, A3, B35, B8  
**Country** United States

**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, escape, variant cross-recognition or cross-neutralization  
**References** Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- The dominant viral sequence was irlrpggRk, found in 12/15 clones, while the screening sequence IRLRPGGKK was found in 3/15 clones. The least frequent variant stimulated the strongest response.
- IRLRPGGKK was previously characterized as a B27 optimized epitope, which is a mismatch with patient's HLA.

**HXB2 Location** p17 (19–27)  
**Author Location**  
**Epitope** IRLRPGGKK



**Immunogen** HIV-1 infection  
**Species (MHC)** human (B2705)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, immunodominance, optimal epitope  
**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope IRLRPGGKK elicited a magnitude of response of 520 SFC with a functional avidity of 0.5nM.

**HXB2 Location** p17 (19–27)  
**Author Location**  
**Epitope** IRLRPGGKK  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox prime with gp120 boost *Strain:* Other *HIV component:* gp160  
**Species (MHC)** human  
**Donor MHC** A3, A33; B15 (63), B27  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes  
**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** p17 (19–28)  
**Author Location** Gag  
**Epitope** IRLRPGGKKK  
**Epitope name** 1271  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11, A3, B62)  
**Donor MHC** A03, A11, B14, B51, Cw08, Cw13  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA  
**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for IRLRPGGKKK:43% Promiscuous epitope binding to A03, B62, Bw62 and A11.

**HXB2 Location** p17 (20–28)  
**Author Location** p17 (20–28)  
**Epitope** RLRPGGKKK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*03)  
**Keywords** review, escape  
**References** Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical sibling hemophiliac brothers were both infected with the same batch of factor VIII.
- They were tested 6-8 years after infection. One had a response to gag A3 epitope RLRPGGKKK, the other non-responder carried the sequence RLRPGGKKC.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

**HXB2 Location** p17 (20–28)  
**Author Location** p17 (20–28)  
**Epitope** RLRPGGKKK  
**Epitope name** RK9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*03)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** binding affinity, subtype comparisons, acute/early infection  
**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this epitope, RK9 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen with both C- and A-clades. Anchor residues are at positions 2 and 9; while the C-clade variant contains a change at position 9 to RLRPGGKKh. Typically, magnitude and avidity of binding for T-cell responses were much lower to the C-clade variant.

**HXB2 Location** p17 (20–28)  
**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes that this is an A\*0301.

**HXB2 Location** p17 (20–28)**Author Location** p17**Epitope** RLRPGGKKK**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Keywords** acute/early infection**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWILGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** p17 (20–28)**Author Location** p17 (20–28 SF2)**Epitope** RLRPGGKKK**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**References** Altfield *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- The reactive peptide p17 gag WEKIRLRPGGKKKYK contained two A\*0301-restricted epitopes, KIRLRPGGK and RLRPGGKKK A\*0301.

**HXB2 Location** p17 (20–28)**Author Location** p17 (20–28)**Epitope** RLRPGGKKK**Epitope name** RK9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Donor MHC** A11, A3, B35, B51**Keywords** mother-to-infant transmission**References** Sabbaj *et al.* 2002

- IFN $\gamma$  T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- Tetramer analysis of breast milk and peripheral blood samples of one volunteer showed responses to RLRPGGKKK in both compartments, 0.65% of CD3+/CD8+ cells in breast milk, and 0.22% of CD3+/CD8+ cells in peripheral blood cells.
- The frequencies of responses in the two compartments differed, and 2/4 women who responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

**HXB2 Location** p17 (20–28)**Author Location** Gag (20–28)**Epitope** RLRPGGKKK**Epitope name** RK9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay**Keywords** escape, acute/early infection, characterizing CD8+ T cells**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- rlrpggkkQ escape mutant showed drastically reduced avidity. The response to this peptide was not apparent until month 20, by month 32 the escape variant was present.

**HXB2 Location** p17 (20–28)**Author Location** p17**Epitope** RLRPGGKKK**Subtype** A**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Donor MHC** A\*0101, A\*0301, B\*0801; A\*0201, A\*3101, B\*3501, B\*3905**Country** United Kingdom**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** escape, acute/early infection, variant cross-recognition or cross-neutralization**References** Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. CTL escape variants were often transmitted. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient.
- Certain escape mutations in RLRPGGKKK, rlrpggkkQ, rlrpggkkR and rlrpggkkT, resulted in nearly complete reduction in binding affinity for A\*0301. The form that was transmitted in one of the donor pairs was rlrpggRkk, and it binds to A\*0301 with comparable affinity to RLRPGGKKK. However, an escape variant was on the rise in the donor near the time of transmission, rlrpggRkT, which eventually came to fixation in the donor, illustrating the importance of the timing of transmission regarding which variant is transmitted.
- A\*0301 epitopes RLRPGGKKK and KIRLRPGGK, and B\*0801 epitope GGKKKYRL, overlap. In 1 donor, the transmitted virus carried the escape form for 2 of these epitopes. The double substitution kirlrpggR results in escape from response in the donor. Similarly, the double substitution ggRkkyKl results in escape for this epitope.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Donor MHC** A\*0101, A\*0301, B\*0801

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, RLRPGGKKK, was found to be 0.032/day, with SE of 0.008.
- The K28T substitution conferred escape from CTL responses of both the RLRPGGKKK and GGKKKYRL epitopes.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Epitope name** RLR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells

**References** Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, A3-RLR (that has no association with accelerated or delayed progression to AIDS) and its natural variants are not cross-recognized. Its alanine-substituted variants were extremely inconsistent between individuals showing very efficient or poor cross-reactivity.

**HXB2 Location** p17 (20–28)

**Author Location** p17

**Epitope** RLRPGGKKK

**Immunogen**

**Species (MHC)** human (A\*0301)

**Country**

**References** Zambia *et al.* 2007

- E169D is a processing mutation for HLA-B\*0702 restricted SPAIFQSSM (SM9) as well as an epitope variation for HLA-A\*0301 restricted MTKILEPFR (MR9).
- CTL recognition of p17 Gag RLRPGGKKK was detected post-infection with either wild type (169E) or mutant 169D HIV-1.

**HXB2 Location** p17 (20–28)

**Author Location**

**Epitope** RLRPGGKKK

**Epitope name** RK9

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (A03)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.

- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p17 (20–28)

**Author Location** Gag (Henan isolate)

**Epitope** RLRPGGKKK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Goulder *et al.* 2000c

- Two clonal CTL responses were generated in donor 021-BMC (HLA A3/3001, B42 $^-$ , Cw17 $^-$ ) against different optimal versions of this epitope, one nine amino acids long, one ten.
- A previously described optimal A3 epitope overlapping this region, KIRLRPGGK, was not recognized by CTL from 021-BMC.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Goulder *et al.* 1997f

- A control CTL line that reacts with this peptide was included in the study.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** subtype comparisons

**References** Cao *et al.* 1997a

- The consensus peptide of A, B, and D clade viruses is RLRPGGKKK.
- The consensus peptide of C clade viruses is RLRPGGKKH and is equally reactive.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (SF2)

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- WEKIRLRPGGKKKYKLLK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – 7/10 that had a dominant response to this epitope were A3, and 5/7 targeted RLRPGGKKK while 2/7 targeted KIRLRPGGK.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28 SF2)

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 5/7 group 1, 2/4 group 2, and 2/2 group 3.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)

- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Epitope name** RK9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** acute/early infection

**References** Goulder *et al.* 2001b

- Responses to this dominant A3-restricted Gag epitope are present during the time of decreasing viral load in acute infection.
- Mutations in this epitope were observed in autologous clones of subjects who were A3-positive with a higher frequency than those who were A3-negative ( $P = 0.0002$ )
- These mutations are being sexually transmitted in adult infections.

**HXB2 Location** p17 (20–28)

**Author Location**

**Epitope** RLRPGGKKK

**Epitope name** Gag-RK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A03, 7/20 (35%) recognized this epitope.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Epitope name** A3-RK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), immunodominance, acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06 was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.

- 8/14 HLA-A3 positive individuals had detectable A3-restricted responses during acute infection. Only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 7/8 individuals with acute responses had specific responses for this epitope.
- KIRLRPGGK and RLRPGGKKK were the most commonly recognized HLA-A3 epitopes during acute infection, after 1 year of treatment, and after STI. RLRPGGKKK was immunodominant during acute infection and throughout the study period in the 5/6 individuals who targeted it.

**HXB2 Location** p17 (20–28)

**Author Location** Gag (LAI)

**Epitope** RLRPGGKKK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** class I down-regulation by Nef

**References** Lewinsohn *et al.* 2002

- CTL kill targets through releasing perforin, that forms pores in the plasma membrane, and granzymes, that induce apoptosis.
- Vpr is capable of arresting infected cells in the G2 phase, and it was hypothesized that Vpr may inhibit CTL-mediated apoptosis because it interacts with the granzyme B molecular complex.
- Vpr expression in the target cell did not inhibit epitope specific lysis – neither perforin or granzyme mediated events were inhibited, as measured by a Chromium release assay and a TUNEL assay.
- In contrast, deletion of Nef, which is thought to protect primary HIV infected cells by down-regulating cell-surface expression of MHC class I complexes, increased the susceptibility of HIV-1 infected cells to CTL mediated killing 2-fold using the TUNEL assay.

**HXB2 Location** p17 (20–28)

**Author Location** p17

**Epitope** RLRPGGKKK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A11, A3, B35, B51

**Keywords** mother-to-infant transmission

**References** Sabbaj *et al.* 2002

- IFN $\gamma$  T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested with using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- T-cells in breast milk from a volunteer who was HLA A3, A11, B35, B51 induced IFN $\gamma$  after stimulation with a peptide that carries known A3 epitope RLRPGGKKK.
- The frequencies of responses in the two compartments differed, and 2/4 women that responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A\*0201, A3, B44, B57, Cw5, Cw6; A1, A3, B14, B7, Cw\*0702, Cw\*0802; A1, A3, B35, B8; A1, A3, B62, B8, Cw3, Cw7

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- This epitope was recognized in four individuals during early infection, each time presented by A3.
- All HIV-1 proteins except Vpu were recognized, and responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Epitope name** A3-RK9 Ga9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant rlrpggkkt. The CTL response declined over time, and the response to the second variant was lower than to the first one throughout.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 5 epitopes from this individual that varied over time where the internal mutations became fixed; 4/5 epitopes (all except p17 RLRPGGKKK, this epitope) showed a dramatic decrease in CTL activity against the wild type epitope as the mutation arose. The rlrpggkkr variant was found at 47 and 120 months post-seroconversion.

**HXB2 Location** p17 (20–28)

**Author Location** Gag

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- 0/5 HLA A3+ infection-resistant men, and 0/3 pre-seroconversion men who went on to become infected, reacted to this epitope.

**HXB2 Location** p17 (20–28)

**Author Location** Gag (20–28)

**Epitope** RPRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, memory cells, characterizing CD8+ T cells

**References** Daniel *et al.* 2004

- CD4+ and CD8+ responses in chronically HIV-1 infected patients on HAART were weak with decreased polyclonality. Only 33% of patients had CD4+ T-cells that could proliferate, and only 22% had HIV-specific CD8+ T-cell responses, and those rare responses showed low perforin levels and persistent

expression of CD27, indicating incomplete differentiation and loss of lytic function.

- HXB2 Location** p17 (20–28)  
**Author Location** p17 (20–28 B consensus)  
**Epitope** RLRPGGKKK  
**Epitope name** RK9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2004
- KK9 and RK9 overlap, are presented by HLA-A3, and are frequently immunodominant and involved in acute-phase primary responses. A mutation in the C-terminal flanking residue of KK9 (K to Q) (kirlrpkkg-Q) inhibits processing of the immunodominant gag KK9 epitope, resulting in rapid decline in the KK9 specific CD8+ T-cell response. At the same time it abrogates the response to RK9 through the embedded mutation rlrpggkQk. Transmission of this mutation to patients expressing HLA-A3 prevents acute-phase response to these epitopes, although the mutation can eventually revert to wild-type allowing a delayed response to the epitope.
- HXB2 Location** p17 (20–28)  
**Author Location** (B consensus)  
**Epitope** RLRPGGKKK  
**Epitope name** RK9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A02, A03, B08, B62, Cw10, Cw7; A01, A03, B08, B14, Cw7, Cw8  
**Country** United States  
**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells  
**References** Lichterfeld *et al.* 2004c
- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
  - 2/9 individuals recognized this epitope, presented by HLA-A3.
- HXB2 Location** p17 (20–28)  
**Author Location** Gag  
**Epitope** RLRPGGKKK  
**Epitope name** RK9

### Subtype B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a
- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - One escape mutation, at position 9, rlrpggkR, was found in the most polymorphic residue in the epitope. This was shared between clades B and C.
- HXB2 Location** p17 (20–28)  
**Author Location** Gag (20–28 BRU)  
**Epitope** RLRPGGKKK  
**Subtype** B, CRF02\_AG  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Country** Cote D'Ivoire  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons  
**References** Inwoley *et al.* 2005
- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivorian subjects.
  - This epitope was recognized by 0/9 CRF02\_AG-infected Ivorians, and 2/9 B-infected French subjects.
- HXB2 Location** p17 (20–28)  
**Author Location** p24  
**Epitope** RLRPGGKKK  
**Epitope name** RK9  
**Immunogen**  
**Species (MHC)** (A3)  
**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion  
**References** Lichterfeld *et al.* 2005
- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.
- HXB2 Location** p17 (20–28)  
**Author Location** p17  
**Epitope** RLRPGGKKK  
**Epitope name** A3-RK9(p17)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p17 (20–28)

**Author Location** Gag

**Epitope** RLRPGGKKK

**Epitope name** 1332

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301, A3, B42, B62)

**Donor MHC** A03, A23, B49, B57; A03, A24, B27, B57, Cw13, Cw18; A03, A26, B08, B52

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction, immunodominance, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for RLRPGGKKK: 34% Promiscuous epitope binding to A03, A0301, B62, Bw62, B42. Immunodominant epitope.

**HXB2 Location** p17 (20–28)

**Author Location** Gag (20–28)

**Epitope** RLRPGGKKK

**Immunogen** peptide-HLA interaction

**Species (MHC)** (A3, A30, A31, A68)

**Assay type** HLA binding

**Keywords** binding affinity, immunodominance

**References** Racape *et al.* 2006

- Interaction between purified HLA-A3 molecules and several dominant CD8 epitopes was characterized. Amplitude, stability, and kinetic parameters of the interaction between HLA-A3, peptides, and anti-HLA mAbs were tested.
- Epitopes tested bound strongly to HLA-A3 and formed very stable complexes.

- Gag epitope RLRPGGKKK and Nef epitope RLAFFHHVAR complexes with HLA-A3 were not recognized by the A11.1 mAb specific to HLA-A3 alleles. The proposed explanation was that Arg at position P1 of the peptide may push the  $\alpha 2$  helix residue and affect mAb recognition.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3, A30, B42, B62)

**Donor MHC** A2, A31, B51, B58w4

**Country** United States

**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, escape, variant cross-recognition or cross-neutralization

**References** Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- The majority of viral sequences prior to therapy were rlrpggkkQ. At week 14 of therapy a major change in the viral quasispecies occurred: the variants present were found to be rlrpggkkK (14/16 clones) and rlrpggkkR (2/16 clones), both well recognized by HIV-specific CD8 T cells. At week 19, the quasispecies reverted back to the less well-recognized rlrpggkkQ variant.

**HXB2 Location** p17 (20–28)

**Author Location** p17 (20–28)

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- Three of the four individuals that responded to SLYNTVATL recognized HIV epitopes, and one individual who was A\*0201, A31 and B51 and B58w4 recognized this epitope (previously described as HLA A3.1), as well as one other.

**HXB2 Location** p17 (20–28)

**Author Location**

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A3, A32; B38, B64

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.



- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- AAVDLSHFL was recognized by a placebo patient after infection.

**HXB2 Location** p17 (20–28)

**Author Location**

**Epitope** RLRPGGKKK

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A\*0201, A\*0301; B\*4501, B\*5301

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** p17 (20–29)

**Author Location** p17 (20–29)

**Epitope** RLRPGGKKKY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**References** Brander & Walker 1995

- Unpublished, C. Jassoy and Beatrice Culman, pers. comm.

**HXB2 Location** p17 (20–29)

**Author Location** p17 (20–29 LAI)

**Epitope** RLRPGGKKKY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**References** Wilkens & Ruhl 1999

- Pers. comm., B. Wilkens and D. Ruhl.

**HXB2 Location** p17 (20–29)

**Author Location** p17 (20–29 LAI)

**Epitope** RLRPGGKKKY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0301 epitope.

**HXB2 Location** p17 (20–29)

**Author Location** (C consensus)

**Epitope** RLRPGGKKHY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RLRPGGKKHY is an optimal epitope.

**HXB2 Location** p17 (20–29)

**Author Location** p17 (20–29)

**Epitope** RLRPGGKKKY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Goulder *et al.* 2000c

- Two clonal CTL responses were generated in donor 021-BMC (HLA A3/3001, B42/-, Cw17/-) against different optimal versions of this epitope, one nine amino acids long, one ten.
- A previously described optimal A3 epitope overlapping this region, KIRLRPGGK, was not recognized by CTL from 021-BMC.

**HXB2 Location** p17 (20–29)

**Author Location** p17

**Epitope** RLRPGGKKKY

**Epitope name** A3-RY11(p17)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p17 (20–29)  
**Author Location** p17 (20–29)  
**Epitope** RLRPGGKKKY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3, A30, B42, B62)  
**Donor MHC** A2, A3, B44, B7  
**Country** United States  
**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, escape, variant cross-recognition or cross-neutralization  
**References** Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- The epitope RLRPGGKKKY was invariant (18/18 sequences) prior to therapy in the patient that recognized it.

**HXB2 Location** p17 (20–29)  
**Author Location** p17 (20–29)  
**Epitope** RLRPGGKKKY  
**Epitope name** RY10  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A30)  
**Donor MHC** A\*24, A\*30, B\*39, B\*47, Cw\*12, Cw\*17; A\*30, B\*18, B\*40, Cw\*02, Cw\*05  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion  
**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- RLRPGGKKKY was recognized in 2 mothers, and is an A\*30 epitope. The variant RLRPGGKKqY was found in 9/10 of 1 mother's sequences. This form was transmitted to her child, and 10/10 clones were this variant at months 2 and 6 in the infant; by month 12, 9/10 were RLRPGGKKqY. RLRPGGKKrY was the form found in the other mother. The variant gradually diminished in frequency in her child, 10/10 sequences at 2 months, 9/10 at 4 months, and 6/10 at 12 months.

**HXB2 Location** p17 (20–29)  
**Author Location** p17 (20–29)  
**Epitope** RLRPGGKKKY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301, A30)  
**Keywords** immunodominance  
**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.

- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was A30, and one was A3, and both responded to RLRPGGKKKY.
- The A2+ A3 individual also reacted with two other A3.1 epitopes.

**HXB2 Location** p17 (20–29)  
**Author Location** p17 (20–29 IIIB)  
**Epitope** RLRPGGKKKY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B42)  
**Keywords** responses in children, mother-to-infant transmission  
**References** Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- RLRPGGKKRY, a naturally occurring variant, was found in non-transmitting mother and is recognized.
- Binds HLA-A3 and Bw62 as well.

**HXB2 Location** p17 (20–29)  
**Author Location** p17 (20–29)  
**Epitope** RLRPGGKKKY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B42, B62)  
**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p17 (20–29)  
**Author Location** p17 (20–29 LAI)  
**Epitope** RLRPGGKKKY  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (B62)  
**Keywords** review  
**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.
- Also P. Johnson, pers. comm.

**HXB2 Location** p17 (20–29)  
**Author Location** p17 (20–29)  
**Epitope** RLRPGGKKKY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B62)  
**References** Brodie *et al.* 2000

- Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL.
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication.
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1 $\alpha$  and MIP-1 $\beta$ , CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism.
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*.

**HXB2 Location** p17 (20–29)  
**Author Location** Gag (20–29)  
**Epitope** RLRPGGKKKY  
**Epitope name** RY10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B62)  
**Donor MHC** A\*01, A\*11, B\*08, B\*15, Cw\*04, Cw\*07  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** escape, variant cross-recognition or cross-neutralization  
**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The RY10 variant RLRPGGrKKY was the only form of the epitope detected over a 5 year time period in this person. Elispot reactions were stronger to the autologous form than to RLRPGGKKKY, the B clade consensus form.

**HXB2 Location** p17 (20–30)  
**Author Location** p17 (SF2)  
**Epitope** RLRPGGKKKYK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons, immunodominance  
**References** Goulder *et al.* 2000a

- WEKIRLRPGGKKKYK was the target of the dominant response in Caucasoids (38%) more frequently than non-Caucasoids (12%) – the dominant response in a Haitian immigrant living in Boston who was HLA A24/29 B7/B44 Cw6/7 was to this epitope, although the restricting element was not determined.
- Three peptides GSEELRSYNTVATL (p17 residues 71–85), SALSEGATPQDLNTMLNTVG (p24 41–60), and WEKIRLRPGGKKKYK (p17 16–30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20–36), ELRSYNTVATLYCV (p17Gag 74–88), SALSEGATPQDLNTMLNTVG (p24 41–60), FRDYVDRFFKTLRAEQA (p24 161–177), and SILDIKQGKEPFRDY (p24 149–164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p17 (20–30)  
**Author Location** Gag (25–35)  
**Epitope** RLRPGGKKHYM  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 3/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p17 (20–35)  
**Author Location** p17 (90–105 SF2)  
**Epitope** CLRPGGKKKYKLRKHIV

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997a
- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
  - Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
  - One of these 12 had CTL response to this peptide.
  - The responding subject was HLA A-2, A-24, B-13, B-35.

**HXB2 Location** p17 (21–35)  
**Author Location** Gag  
**Epitope** LRPGGKKKYKLRKHIV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Keywords** TCR usage  
**References** Weekes *et al.* 1999b

- Peptide 703.3: Almost all CD8+ T cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed in the CD28 depleted cell population.
- HIV CTL responses to 3 Env and 2 Gag peptides were studied.
- The clonal composition of the TCR V $\beta$  responses was studied and was found to be highly focused, with one TCR beta-chain sequence tending to dominate the peptide-specific response – clones to this epitope were V $\beta$ 13.1 and V $\beta$ 5.2.

**HXB2 Location** p17 (21–35)  
**Author Location** p17 (21–35)  
**Epitope** LRPGGKKKYKLRKHIV

- Epitope name** Peptide 703.3  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A2, A3, B44, B7  
**Country** United Kingdom  
**Assay type** Flow cytometric T-cell cytokine assay, Other  
**Keywords** HAART, ART, immunodominance, TCR usage, memory cells  
**References** Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintenance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced clonal efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

**HXB2 Location** p17 (21–35)

**Author Location** p17 (21–35)

**Epitope** LRPGGKKKYKLNHIV

**Immunogen**

**Species (MHC)** human (B8)

**References** Nixon & McMichael 1991

- Two CTL epitopes defined (see also p24(191-205))

**HXB2 Location** p17 (21–35)

**Author Location** p17 (21–35)

**Epitope** LRPGGKKKYKLNHIV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, LRPGGKKKYKLNHIV, was found to be -0.001/day (upper bound on rate of escape = 0.085), with SE of 0.003.
- In the subject studied, K26R grew out steadily to 95% frequency, but then there was a progressive re-emergence of the wild type. If data from all time points were fitted, then the mutant actually had a negative growth rate because it was eventually out-competed by the wild type.

**HXB2 Location** p17 (21–35)

**Author Location** p17 (21–35)

**Epitope** LRPGGKKKYKLNHIV

**Immunogen** HIV-1 infection

**Species (MHC)** human (not B8)

**References** van Baalen *et al.* 1996

- Unknown HLA specificity, but not B8.

**HXB2 Location** p17 (21–35)

**Author Location** Gag

**Epitope** LRPGGKKKYKLNHIV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Weekes *et al.* 1999a

- Peptide 703.3: Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28- CD8+ CTL populations.

**HXB2 Location** p17 (21–35)

**Author Location** p17 (91–105 SF2)

**Epitope** LRPGGKKKYKLNHIV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A1, A2, B50, B57.

**HXB2 Location** p17 (21–35)

**Author Location** p17 (24–31)

**Epitope** LRPGGKKKYRLKHLV

**Subtype** A, D

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*6601, A\*6801, B\*5301, B\*5802; A\*3002, A\*6801, B\*5703, B\*5802

**Country** Uganda

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

**References** Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- The sequence contains a known B8 epitope, but the subjects recognizing it were B8-negative. The autologous viral sequence was lrpggkkyKlkhiv, and the peptide was recognized.

**HXB2 Location** p17 (21–40)

**Author Location** p17 (21–40 subtype A)

**Epitope** LRPGGKKKYRLKHLVWASRE

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw4)

**Keywords** subtype comparisons

**References** Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa.
- This epitope was defined in an A subtype infection – the B clade variant (LRPGGKKKYKLLKHIVWASRE) has two mutations relative to the A subtype form, and the CTLs from this patient were not A-B cross-reactive.

**HXB2 Location** p17 (22–29)

**Author Location** Gag (22–29)

**Epitope** RPPGKKHY

**Subtype** A, C, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07, B\*42)

**Country** Tanzania

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, immunodominance

**References** Geldmacher *et al.* 2007a

- To assess whether T-cell specific responses to Gag and Nef are biased towards infecting subtype recombination, 56 ART-naive subjects were studied using six overlapping peptide sets consisting 15-mer peptides, covering both proteins completely. A multi-region hybridization assay was employed. Overall, the best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants RPPGKKhY, RPPGKKkY and RPPGKKqY were studied as peptide sequences EKIRL-RPPGKKhY-ML (subtype C), EKIRL-RPPGKKkY-RL (subtypes A and D) and EKIRL-RPPGKKqY-RM with 12.5% responders. Subtype A was best recognized.

**HXB2 Location** p17 (22–30)

**Author Location** p17 (22–30)

**Epitope** RPPGKKRYM

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35, Cw\*0602)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- This is a novel epitope that may be subtype C-specific.

**HXB2 Location** p17 (22–31)

**Author Location** Gag (22–31)

**Epitope** RPPGKKKYML

**Subtype** A, C, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702, B\*5801, B\*8101)

**Country** Tanzania

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** rate of progression, immunodominance

**References** Geldmacher *et al.* 2007b

- The objectives of this study were to find antiviral epitopic determinants of Gag HIV-specific CTL response and to find 'host HLA-CTL response' correlations. By studying 56 ART-naive subjects including low viral load (LVL) responders, the authors show that subjects expressing the above "protective" HLA have broader Gag epitope recognition which may be abrogated if co-expressed with HLA-B alleles associated with rapid AIDS progression. Also, a negative linear relation was seen between Gag epitope numbers recognized and plasma viral load while a positive relationship was seen with CD4 T-cell count. Finally, LVL subjects recognized specific Gag regions at the N- and C-termini of the protein more often than peptides in the middle of the protein.
- Epitope RPPGKKKYML, presented by HLA-B\*0702 and B\*4201 is strongly associated with LVL. However, the last position RPPGKKKYMI is highly variable.

**HXB2 Location** p17 (22–31)

**Author Location** Gag (22–31)

**Epitope** RPPGKKRYKL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Jin *et al.* 2000b

- This B7 epitope is one of three subdominant CTL responses detected in a long-term non-progressor.
- A dominant B7 epitope was defined using conventional methods, and three additional sub-dominant HLA B7 epitopes were defined by first using a non-anchor based strategy, EpiMatrix, to identify 2078 possible epitopes in the autologous HIV-1, followed by B7 anchor residue prediction to narrow the set to 55 peptides for experimental testing.

**HXB2 Location** p17 (22–31)

**Author Location** p17

**Epitope** RPPGKKKYKL

**Subtype** B, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw4)

**Donor MHC** A23, A34, B44, B53, Cw4, Cw6

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse

correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.

- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence had an K5N change, RPPGnKKYKL.

**HXB2 Location** p17 (24–31)

**Author Location** p17

**Epitope** GGKKKYKL

**Epitope name** GL8

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Donor MHC** A\*0101, A\*0301, B\*0801; A\*0201, A\*3101, B\*3501, B\*3905

**Country** United Kingdom

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** escape, acute/early infection, variant cross-recognition or cross-neutralization

**References** Milicic *et al.* 2005

- Escape mutation ggRkkyKl in this epitope, GGKKKYRL, resulted in failure of recognition by CTLs, and the ggkkQyRl mutations resulted in 82% reduction in HLA binding affinity.
- A\*0301 epitopes RLRPGGKKK and KIRLRPGGK, and B\*0801 epitope GGKKKYRL, overlap. In 1 donor, the transmitted virus carried the escape form for 2 of these epitopes. The double substitution kirlrpggR results in escape from response in the donor. Similarly, the double substitution ggRkkyKl results in escape for this epitope.

**HXB2 Location** p17 (24–31)

**Author Location** p17 (24–31)

**Epitope** GGKKKYRL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Donor MHC** A\*0101, A\*0301, B\*0801

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms

of absolute numbers of infected cells killed, which are likely to be clinically relevant.

- The best estimate of escape rate for this epitope, GGKKKYRL, was found to be 0.032/day, with SE of 0.008.
- The K28T substitution conferred escape from CTL responses of both the RLRPGGKKK and GGKKKYRL epitopes.

**HXB2 Location** p17 (24–31)

**Author Location** p17 (24–31)

**Epitope** GGKKKYKL

**Immunogen**

**Species (MHC)** human (B8)

**References** Goulder *et al.* 1997g

- The crystal structure of this peptide bound to HLA-B8 was used to predict new epitopes and the consequences of epitope variation.
- The predictions were experimentally confirmed.
- The anchors for HLA-B8 epitopes, as defined by peptide elution data, are P3 (K), P5 (K/R), and P8 (L).
- Structural data suggests that a positive charge at P5 is essential, but that the constraints on P3 may be less severe.
- Small hydrophobic residues at P2 may be favorable for binding.
- A spacious F-pocket favors mid-sized hydrophobic residues in the C-term anchor.

**HXB2 Location** p17 (24–31)

**Author Location** p17 (24–31 SF2)

**Epitope** GGKKKYKL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** subtype comparisons

**References** McAdam *et al.* 1998

- CTL from a patient infected with clade B virus did not recognize Ugandan variants of this epitope.

**HXB2 Location** p17 (24–31)

**Author Location** p17 (24–31 LAI)

**Epitope** GGKKKYKL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** TCR usage

**References** Reid *et al.* 1996

- The variants 7R: GGKKKYRL, 7Q: GGKKKYQL, 5R: GGKKRYKL, and 3R: GGRKKYKL, were studied.
- Crystal structures were obtained to study these peptides in the context of HLA-B8, and CTL binding and activity were determined.
- 3R has been detected in 3 patients, and it abolishes recognition causing extensive conformational changes upon binding including MHC main chain movement.
- 7Q and 7R alter the TCR exposed surface, and retain some recognition.
- Reactivity of 5R depends on the T cell clone, this amino acid is embedded in the C pocket of B8 when the peptide is bound.
- Optimal peptide is 8-mer, not 9-mer, and positions 3, 5, and 8 are the anchor residues.

**HXB2 Location** p17 (24–31)  
**Author Location** p17 (24–31 LAI)  
**Epitope** GGKKKYKL  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Price *et al.* 1997

- A weak CTL response to the index peptide was observed in an HLA-B8+ infected individual.
- Sequences from the earliest available time point showed that a variant at position 5, an anchor residue, GGKKQYKL, was present.

**HXB2 Location** p17 (24–31)  
**Author Location** p17

**Epitope** GGKKKYKL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** HAART, ART  
**References** Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.
- In Figure 4 legend, epitope GGKKKkYKL is printed as having been used. We chose to record the epitope as GGKKKYKL seen elsewhere in this paper, as it is more commonly annotated as such in the literature.

**HXB2 Location** p17 (24–31)  
**Author Location** p17 (24–31 SF2)  
**Epitope** GGKKKYKL

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 1/3 group 2, and 2/2 group 3.

**HXB2 Location** p17 (24–31)  
**Author Location** p17 (24–31)  
**Epitope** GGKKKYRL

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (B8)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** p17 (24–31)  
**Author Location** p17 (24–31)

**Epitope** GGKKKYKL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

**HXB2 Location** p17 (24–31)  
**Author Location** p17

**Epitope** GGKKKYKL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)

- Keywords** binding affinity, review, subtype comparisons, epitope processing, escape
- References** McMichael & Hanke 2002
- CTL response-eliciting vaccines are reviewed. The natural epitope interactions with the HLA class I presenting molecules and T-cell receptors are described, using the structure of this epitope, taken from Reid *et al.* [1996], as an example.

**HXB2 Location** p17 (24–31)  
**Author Location** (B consensus)

**Epitope** GGKKKYKL  
**Epitope name** GL8  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Donor MHC** A01, A03, B08, B14, Cw7, Cw8  
**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** p17 (24–31)  
**Author Location** p17

**Epitope** GGKKKYKL  
**Subtype** B, D  
**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A1A1, B55, B8, Cw3, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence had an L8M change, GGKKKYKm.

**HXB2 Location** p17 (24–31)

**Author Location** Gag (24–31 BRU)

**Epitope** GGKKKYKL

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivorian subjects.
- This epitope was recognized by 1/9 CRF02\_AG-infected Ivorians, and 0/9 B-infected French subjects.

**HXB2 Location** p17 (24–31)

**Author Location** p17 (24–31)

**Epitope** GGKKKYKL

**Epitope name** GL8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A\*03, A\*31, B\*08, B\*15, Cw\*04, Cw\*07

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in

the infant over time was determined by infant HLA haplotype and viral fitness.

- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- Variant sequence ggRkkykl was present in 10/10 clones from a B8-positive mother, but decreased to 0/10 clones by 15 months of age in her B8-negative child.
- The variant ggRkkykl was present in 10/10 clones from a B8+ mother, was transmitted to her infant, and present in 10/10 clones at months 2 and 4, but decreased to 0/10 clones by 15 months of age in her B8- child.

**HXB2 Location** p17 (24–31)

**Author Location** p17 (24–31 HXB2)

**Epitope** GGKKKYKL

**Epitope name** GL8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A\*0101, A\*0201, B\*0801, B\*50, Cw\*0602, Cw\*0701

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, viral fitness and reversion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Gag epitope GGKKKYKf (p17-31F) presumed escape variant was transmitted from a B8 positive donor to a B8 negative recipient. Reversions to GGKKKYKl were found in the recipient.

**HXB2 Location** p17 (24–31)

**Author Location**

**Epitope** GGKKKYKL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade MN *HIV component:* gp160

**Species (MHC)** human

**Donor MHC** A1, A33; B44, B8

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.



- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** p17 (24–32)  
**Author Location** p17 (24–32 LAI)  
**Epitope** GGKKKYKLLK  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes epitope to be presented by B\*0801.

**HXB2 Location** p17 (24–32)  
**Author Location** p17 (24–32)  
**Epitope** GGKKKYKLLK

- Epitope name** GGK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells  
**References** Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B8-GGK and its alanine-substituted variants are very weakly cross-recognized and reactive.

**HXB2 Location** p17 (24–32)  
**Author Location** p17 (24–32 LAI)  
**Epitope** GGKKKYKLLK  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Sutton *et al.* 1993
- Exploration of HLA-B8 binding motif through peptide elution.

**HXB2 Location** p17 (24–32)  
**Author Location** p17 (24–32 LAI)  
**Epitope** GGKKKYKLLK  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** epitope processing  
**References** Rowland-Jones *et al.* 1993
- Study of an individual with partially defective antigen processing.

- HXB2 Location** p17 (24–32)  
**Author Location** p17 (24–32)  
**Epitope** GGKKKYKLLK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Klenerman *et al.* 1994
- Naturally occurring variants GGKKKYQLK and GGKKRYRLK may act as antagonists.

- HXB2 Location** p17 (24–32)  
**Author Location** p17 (24–32)  
**Epitope** GGKKKYKLLK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Klenerman *et al.* 1995
- Naturally occurring antagonist GGKKKYQLK found in viral PBMC DNA and RNA.

- HXB2 Location** p17 (24–32)  
**Author Location** p17 (24–32)  
**Epitope** GGKKKYKLLK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** escape  
**References** Nowak *et al.* 1995
- Longitudinal study of CTL response and immune escape – the variant GGRKKYKLLK binds to HLA-B8 but is not reactive.

- HXB2 Location** p17 (24–32)  
**Author Location** p17 (24–32)  
**Epitope** GGKKKYKLLK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Dyer *et al.* 1999
- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 that was Nef-defective.
  - Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

- HXB2 Location** p17 (24–32)  
**Author Location** p17  
**Epitope** GGKKKYKLLK  
**Immunogen**  
**Species (MHC)** human (B8)  
**References** Rowland-Jones *et al.* 1999
- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
  - In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.

- HIV-2 sequence: GGKKKYKMK – no cross-reactivity Phillips *et al.* [1991].

**HXB2 Location** p17 (24–32)

**Author Location** p17 (24–32)

**Epitope** GGKKKYKMK

**Epitope name** GGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- This epitope was recognized by 1/7 study subjects that were HLA-B8+.
- Patient SC12(HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKR-WII, DCKTILKAL, GGKKKYKMK – GEIYKRWII and GGKKKYKMK responses were stimulated by a brief period off therapy.

**HXB2 Location** p17 (24–32)

**Author Location** p17

**Epitope** GGKKKYKMK

**Epitope name** GGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** p17 (24–32)

**Author Location** p17

**Epitope** GGKKKYKMK

**Epitope name** B8-GK9(p17)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.

- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p17 (24–32)

**Author Location**

**Epitope** GGKKKYKMK

**Immunogen**

**Species (MHC)** (B8)

**Keywords** review, immunodominance, escape, vaccine antigen design

**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.

- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection (recognized by about 20% of subjects).

**HXB2 Location** p17 (24–35)

**Author Location** p17 (25–35 SF2)

**Epitope** GGKKKYKMKHIV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** review, immunodominance, escape

**References** Goulder *et al.* 1997a; Phillips *et al.* 1991

- Longitudinal study of CTL escape mutants in people with the appropriate HLA types – little variation was observed in the immunodominant B27 epitope, relative to B8 epitopes, which varied over time.

- Goulder *et al.* [1997a] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA-B27 patients.

**HXB2 Location** p17 (24–35)

**Author Location** p17 (25–35)

**Epitope** GGKKKYKMKHIV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

**HXB2 Location** p17 (27–35)

**Author Location** p17 (27–35)

**Epitope** KRYMIKHLV

**Subtype C****Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0602)**Country** India**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, computational epitope prediction, immunodominance**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope KRYMIKHLV was conserved only across clade C.

**HXB2 Location** p17 (28–36)**Author Location** (C consensus)**Epitope** HYMLKHIVW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2301)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the M in the third residue HYMLKHIVW are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** p17 (28–36)**Author Location** Gag (28–36)**Epitope** HYMLKHIVW**Subtype** A, C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2301)**Country** Tanzania**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** subtype comparisons, immunodominance**References** Geldmacher *et al.* 2007a

- To assess whether T-cell specific responses to Gag and Nef are biased towards infecting subtype recombination, 56 ART-naive subjects were studied using six overlapping peptide sets consisting 15-mer peptides, covering both proteins completely. A multi-region hybridization assay was employed. Overall, the best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17

and p15; hotspots against Nef were in its central, conserved region.

- Epitope variants hYmLKHIVW, kYrLKHIVW and qYrLKHIVW were studied as peptide sequences GKK-hYmLKHIVW-ASR (subtype C), GKK-kYrLKHIVW-ASR (subtype A) and GKK-qYrLKHIVW-ASR with 21% responders. Subtype C epitopes were best recognized.

**HXB2 Location** p17 (28–36)**Author Location** (C consensus)**Epitope** HYMLKHLVW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2301, A\*2402)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** cross-presentation by different HLA, characterizing CD8+ T cells**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p17 (28–36)**Author Location** p17 (28–36 LAI)**Epitope** KYLKLKHIVW**Subtype** B**Immunogen****Species (MHC)** human (A\*2402)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes that this is an A\*2402 epitope.

**HXB2 Location** p17 (28–36)**Author Location** p17 (28–36 SF2)**Epitope** KYLKLKHIVW**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2402)**References** Ikeda-Moore *et al.* 1998

- Strong CTL activity to this peptide was detected in 2/3 HIV-infected individuals who were HLA A24+.
- HLA A24 is very common in Japanese (70% carry it) and is common globally.
- This epitope was detected by looking for peptides with appropriate A24 anchor residues (Y at position 2, carb-term ILF or W) – 16/17 such peptides bound to A24 – KYLKLKHIVW was found to be a naturally processed epitope that elicits a strong CTL response.

**HXB2 Location** p17 (28–36)**Author Location** (28–36)

**Epitope** HYMLKHLVW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2402)**Assay type** Other**Keywords** HLA associated polymorphism**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- HYMLKHLVW was a previously defined A\*2402 presented epitope that encompassed an A\*24 associated polymorphism, HYmLKHLVW, in the third position.

**HXB2 Location** p17 (28–36)**Author Location** p17**Epitope** KYCLKHIVW**Immunogen** peptide-HLA interaction**Species (MHC)** human (A\*2402)**Assay type** Tetramer binding**Keywords** binding affinity**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, KYCLKHIVW (MHC Class I restriction, serotype Bw4) complexed with MHC A\*2402 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C. However, the A\*2402-KYCLKHIVW complex does bind inhibitory KIR3DL1 subtype KIR3DL1\*005.

**HXB2 Location** p17 (28–36)**Author Location** p17 (28–36 LAI)**Epitope** KYCLKHIVW**Subtype** B**Immunogen****Species (MHC)** human (A23)**References** Goulder & Walker 1999

- P. Goulder, pers. comm.

**HXB2 Location** p17 (28–36)**Author Location** p17 (28–36 LAI)**Epitope** KYCLKHIVW**Subtype** B**Immunogen****Species (MHC)** human (A24)**References** Brander & Walker 1996

- D. Lewinsohn, pers. comm.

**HXB2 Location** p17 (28–36)**Author Location** p17 (28–36 SF2)**Epitope** KYCLKHIVW**Immunogen** HIV-1 infection**Species (MHC)** human (A24)**Keywords** HAART, ART, acute/early infection**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A24+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 2/3 group 2, and 0/0 group 3.

**HXB2 Location** p17 (28–36)**Author Location** p17 (28–36 93TH253 subtype CRF01)**Epitope** KYCLKHIVW**Subtype** CRF01\_AE**Immunogen** HIV-1 infection**Species (MHC)** human (A24)**Keywords** subtype comparisons**References** Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- The only HLA-A24 FSWs tested did not recognize the E clade version of this epitope KYKMKHLVW, which differs from the previously defined B clade version by two amino acids, KYCLKHIVW.

**HXB2 Location** p17 (28–36)**Author Location** p17**Epitope** KYCLKHIVW**Epitope name** KW9**Immunogen** HIV-1 infection**Species (MHC)** human (A24)**Donor MHC** A2, A24, B38, B60, Cw12, Cw2**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** supervised treatment interruptions (STI), acute/early infection**References** Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

**HXB2 Location** p17 (28–36)

**Author Location** p17 (28–36)

**Epitope** KYKCLKHIVW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A\*0201, A\*2402, B\*52, B75, Cw\*03; A\*0207, A\*2402, B\*46, B\*52, Cw\*01; A\*2402, A\*26, B\*07, B\*5101, Cw\*07

**Country** Japan

**Assay type** Chromium-release assay

**Keywords** epitope processing, escape

**References** Yokomaku *et al.* 2004

- Epitope variants escaped from being killed by CTLs in an endogenous expression system although they were recognized when corresponding synthetic peptides were exogenously loaded onto the cells. Escape is thus probably due to changes that occur during the processing and the presentation of epitopes in infected cells.
- Epitope variants recognized when added exogenously but not when processed endogenously were: kyRlkhLvw, RyRlkhLvw and QyRlkhivw.

**HXB2 Location** p17 (28–36)

**Author Location** p17 (28–36)

**Epitope** KYKCLKHIVW

**Epitope name** QW9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A\*24, A\*30, B\*39, B\*47, Cw\*12, Cw\*17; A\*23, A\*24, B\*07, B\*39, Cw\*12, Cw\*17

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion

**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.

- qYKCLKHIVW is an escape variant of the A\*24 epitope KYKCLKHIVW, found in 9/10 clones from the mother. It was transmitted to her infant, and persisted for 15 months. Both the mother and child are A\*24+.
- qYKCLKHIVW elicited lower responder cell frequencies than KYKCLKHIVW.

**HXB2 Location** p17 (28–36)

**Author Location** p17

**Epitope** KYKCLKHIVW

**Epitope name** A24-KW9(p17)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p17 (28–36)

**Author Location**

**Epitope** KYKCLKHIVW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (A24), an additional HLA (A23) was statistically predicted to be associated with this epitope.

**HXB2 Location** p17 (28–36)

**Author Location** Gag (28–36)

**Epitope** HYMLNHIVW

**Subtype** A, C, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702, B\*5801, B\*8101)

**Country** Tanzania

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** rate of progression, immunodominance

**References** Geldmacher *et al.* 2007b

- The objectives of this study were to find antiviral epitopic determinants of Gag HIV-specific CTL response and to find 'host HLA-CTL response' correlations. By studying 56 ART-naive subjects including low viral load (LVL) responders, the authors show that subjects expressing the above "protective" HLA have broader Gag epitope recognition which may be abrogated if co-expressed with HLA-B alleles associated with rapid AIDS progression. Also, a negative linear relation was seen between Gag epitope numbers recognized and plasma viral load while a positive relationship was seen with CD4 T-cell count. Finally, LVL subjects recognized specific Gag regions at the N- and C-termini of the protein more often than peptides in the middle of the protein.
- Epitope HYMLNHIVW is overrepresented for recognition within the LVL group. However, this immunodominant epitope is most variable of all.

**HXB2 Location** p17 (28–36)

**Author Location** p17 (728–736 subtype A)

**Epitope** KYRLKHLVW

**Subtype** A

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (Cw4)

**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-Cw4 women, 2/2 HEPS and 7/11 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in both of the 2/2 HEPS cases and in 3 of the 7/11 HIV-1 infected women.

**HXB2 Location** p17 (28–36)

**Author Location** p17 (28–36)

**Epitope** KYRLKHLVW

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw4)

**References** Appay *et al.* 2000

- This epitope is newly defined in this study.

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.

- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.

- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$ .

**HXB2 Location** p17 (28–36)

**Author Location**

**Epitope** KYRLKHLVW

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.

- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.

- This epitope was recognized in 1/22 HEPS sex worker controls (ML1573).

**HXB2 Location** p17 (28–38)

**Author Location** Gag (33–43)

**Epitope** HYMLKHLVWAS

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.

- 1/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p17 (32–46)

**Author Location** p17

**Epitope** KHIWVASRELERFAV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, KHIVWASRELERFAV, had an overall frequency of recognition of 16.7% - 23.7% AA, 19.2% C, 9.1% H, 4.8% WI.

**HXB2 Location** p17 (33–41)**Author Location** p17 (33–41)**Epitope** HLVWASREL**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0602)**Country** India**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, computational epitope prediction, immunodominance**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- This is a novel predicted epitope with >80% conservation to subtype A.

**HXB2 Location** p17 (33–41)**Author Location** p17**Epitope** HLVWASREL**Epitope name** HL-9**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0804)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay**Keywords** subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA**References** Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. This is 1 of 5 novel epitopes that were found among subtype C HIV-1 from African patients who hadn't previously been identified in B clade infections. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles.
- HLVWASREL was presented by Cw\*08 and newly identified in this study; Cw\*08 is slightly more common in Zulus than Caucasians (0.066 versus 0.038).

**HXB2 Location** p17 (33–41)**Author Location****Epitope** HLVWASREL**Immunogen****Species (MHC)** human (Cw\*0804)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes that this is an Cw\*0804 epitope.

**HXB2 Location** p17 (34–43)**Author Location** Gag (Henan isolate)**Epitope** IVWASRELER**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A11)**Country** China**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (34–44)**Author Location** p17**Epitope** LVWASRELERF**Epitope name** LF-11**Subtype** C**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002, B\*570301)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA

**References** Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. This is 1 of 5 novel epitopes that were found among subtype C HIV-1 from African patients who hadn't previously been identified in B clade infections. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles.
- LVWASRELERF was clearly presented by both A\*3002 and B\*570301, it might also be cross-presented by A\*3001, but not as effectively. A\*30 is 10-fold more common among Zulus than Caucasians (allele frequency 0.195 versus 0.019), while B\*57 is similar (0.051 versus 0.043).

**HXB2 Location** p17 (34–44)

**Author Location** p17 (34–44)

**Epitope** LVWRELERF

**Immunogen**

**Species (MHC)** human (A30)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an A30 epitope.

**HXB2 Location** p17 (34–44)

**Author Location** (C consensus)

**Epitope** LVWASRELERF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5703)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- LVWASRELERF is an optimal epitope.

**HXB2 Location** p17 (34–44)

**Author Location** (C consensus)

**Epitope** LVWASRELERF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p17 (36–44)

**Author Location** p17 (35–43 LAI)

**Epitope** WASRELERF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**References** Goulder *et al.* 1997d

- Optimal epitope defined from within p17(30-44), LKHIVWASRELERFA.
- Dominant CTL response in an HIV+ asymptomatic donor was to this epitope.
- The Phe in the C-term anchor is distinct from the previously-defined Tyr for B\*3501 C-term anchors.

**HXB2 Location** p17 (36–44)

**Author Location** p17 (36–44 LAI)

**Epitope** WASRELERF

**Subtype** B

**Immunogen**

**Species (MHC)** human (B\*3501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008; Goulder *et al.* 1997b

- C. Brander notes this is a B\*3501 epitope.

**HXB2 Location** p17 (36–44)

**Author Location** p17 (36–44)

**Epitope** WASRELERF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

**HXB2 Location** p17 (36–44)

**Author Location** p17 (36–44)

**Epitope** WASRELERF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p17 (36–44)

**Author Location** p17 (36–44 SF2)

**Epitope** WASRELERF



- Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b
- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
  - The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
  - Previously described and newly defined optimal epitopes were tested for CTL response.
  - Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 0/2 group 2, and 1/1 group 3.

**HXB2 Location** p17 (36–44)

**Author Location**

**Epitope** WASRELERF

**Epitope name** Gag-WF9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 1/21 (5%) recognized this epitope.

**HXB2 Location** p17 (36–44)

**Author Location** Gag

**Epitope** WASRELERF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- No one, 0/3 HLA B35+ infection-resistant men, and 0/5 pre-seroconversion men who went on to become infected, reacted to this epitope.

**HXB2 Location** p17 (36–44)

**Author Location**

**Epitope** WASRELERF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope WASRELERF elicited a magnitude of response of 220 SFC with a functional avidity of 0.01nM and binding affinity of 17432nM.

**HXB2 Location** p17 (36–44)

**Author Location**

**Epitope** WASRELERF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B35), an additional HLA (B53) was statistically predicted to be associated with this epitope.

**HXB2 Location** p17 (36–44)

**Author Location** p17 (36–44)

**Epitope** WASRELERF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0602)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.

- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope WASRELERF showed >80% conservation with subtypes B and D.

**HXB2 Location** p17 (36–44)

**Author Location** p17 (SF2)

**Epitope** WASRELERF

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The dominant response in an African American who was HLA A3/33 B35/B53 Cw4/7 was to this epitope, although the restricting element was not determined – this epitope fell outside the most recognized peptides in the study.
- Three peptides GSEELRSYNTVATL (p17 residues 71–85), SALSEGATPQDLNLTMLNTVG (p24 41–60), and WEKIRLRPGGKKKYK (p17 16–30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20–36), ELRSYNTVATLYCV (p17Gag 74–88), SALSEGATPQDLNLTMLNTVG (p24 41–60), FRDYVDRFFKTLRAEQA (p24 161–177), and SILDIKQGKPEFRDY (p24 149–164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p17 (37–51)

**Author Location** p17

**Epitope** ASRELERFAVNPGLL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved

peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J. Virol.* 76:8757–68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This overlapping peptide, ASRELERFAVNPGLL, was differentially targeted across ethnic groups and had an overall frequency of recognition of 13.3% - 6.8% AA, 26.9% C, 20.5% H, 0% WI (P value = 0.0068).

**HXB2 Location** p17 (43–51)

**Author Location** p17

**Epitope** RFAVNPGLL

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B63)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, cross-presentation by different HLA

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63 epitope is contained within a reactive peptide containing the B58 supertype binding motif. There is no evidence for B57/B58 cross-presentation of this epitope.

**HXB2 Location** p17 (49–57)

**Author Location** Gag (Henan isolate)

**Epitope** GLLESSEGC

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (59–67)

**Author Location** Gag (Henan isolate)

- Epitope** QILEQLQPA  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006
- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- HXB2 Location** p17 (59–68)  
**Author Location** Gag (Henan isolate)  
**Epitope** QILEQLQPAL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006
- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- HXB2 Location** p17 (63–72)  
**Author Location** p17 (63–72)  
**Epitope** QLQPSLQTGS  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007
- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.

- This epitope, QLQPSLQTGS, was detected within overlapping peptides QLQPSLQTGSEELRSly and EGCRQILQLQPSLQTGS.

**HXB2 Location** p17 (69–93)  
**Author Location** p17 (69–93 BH10)  
**Epitope** QTGSEELRSlyNTVATLYCVHQRIE

- Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Johnson *et al.* 1991
- Gag CTL response studied in three individuals.

**HXB2 Location** p17 (70–86)  
**Author Location** p24  
**Epitope** TGSEELRSlyNTVATLY  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J.Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, TGSEELRSlyNTVATLY, had an overall frequency of recognition of 22% - 23.7% AA, 23.1% C, 22.7% H, 4.8% WI. This peptide is included in a 34 aa Gag-p17 highly reactive region to be used for vaccine design.

**HXB2 Location** p17 (71–79)  
**Author Location** Gag (71–79)  
**Epitope** GSEELRSly  
**Epitope name** GY9

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (A\*01)**Donor MHC** A\*02, B\*08**Country** United States**Assay type** Intracellular cytokine staining, Other**Keywords** rate of progression, escape, immune evasion**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naïve subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- In one patient, this epitope GSEELRSLY varied at Y79F to GSEELRSLF, at an anchor position, conferring potent viral escape. One other variant seen was GSEELRSLc.

**HXB2 Location** p17 (71–79)**Author Location** p17**Epitope** GTEELRSLY**Subtype** A**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0101)**Donor MHC** A\*0101, A\*0301, B\*0801; A\*0201, A\*3101, B\*3501, B\*3905**Country** United Kingdom**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** escape, acute/early infection, characterizing CD8+ T cells**References** Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- Escape mutation gteelrslF in this epitope resulted in 98% reduction in HLA binding affinity, and was the transmitted variant.

**HXB2 Location** p17 (71–79)**Author Location** p17**Epitope** GSEELRSLY**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0101)**Donor MHC** A\*0101, A\*0301, B\*0801, B\*5101; A\*0101, B\*0801**Country** United Kingdom**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** escape, acute/early infection, characterizing CD8+ T cells**References** Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. CTL escape variants were often transmitted. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient.
- The second donor in the study shares A\*0101 and B\*0801 with his partner. Escape mutations gseeIKsly in GSEELRSLY resulted in 44% reduction in HLA binding affinity and no response in an Elispot assay, and gseeIKsly was the transmitted form.

**HXB2 Location** p17 (71–79)**Author Location** p17 (71–79 LAI)**Epitope** GSEELRSLY**Subtype** B**Immunogen****Species (MHC)** human (A1)**References** Brander & Walker 1996

- P. Goulder, pers. comm.

**HXB2 Location** p17 (71–79)**Author Location** p17 (71–79)**Epitope** GSEELRSLY**Immunogen** HIV-1 infection**Species (MHC)** human (A1)**References** Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

**HXB2 Location** p17 (71–79)**Author Location** p17 (71–79 HXB2)**Epitope** GSEELRSLY**Epitope name** GSE**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A1)**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses

and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.

- This epitope was not recognized by the 6/8 study subjects that were HLA-A1.

**HXB2 Location** p17 (71–79)

**Author Location** p17 (71–79)

**Epitope** GSEELRSLY

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A1)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A1 women, 1/1 HEPS and 3/3 HIV-1 infected women recognized this epitope, and the response was the dominant HLA-A1 response in all cases.

**HXB2 Location** p17 (71–79)

**Author Location** p17

**Epitope** GSEELRSLY

**Epitope name** GSE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with supervised treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** p17 (71–79)

**Author Location** p17 (71–79)

**Epitope** GSEELRSLY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.

- 3/13 patients recognized this epitope.

**HXB2 Location** p17 (71–79)

**Author Location** (71–79 B consensus)

**Epitope** GSEELRSLY

**Epitope name** GY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** characterizing CD8+ T cells

**References** Allen *et al.* 2004

- This study characterizes an escape mutation in a C-terminal flanking residue of the HLA-A3 gag p17 KK9 epitope that inhibits processing, and is embedded in the overlapping HLA-A3 RK9 epitope.
- The immune response was tracked in subject AC-38. The acute immunodominant response was to the B57 TW10 epitope; this response declined following viral escape (tsNlqeqigw) by day 64. The p17 KK9 and RK9 became immunodominant, but then declined as the escape mutation arose. Three other strong responses that persisted were detected, along with 1 sub-dominant response to GY9.

**HXB2 Location** p17 (71–79)

**Author Location** Gag

**Epitope** GSEELRSLY

**Epitope name** GL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 9, gseelrIF, was found in the most polymorphic residue in the epitope. These were shared between clades B and C.

**HXB2 Location** p17 (71–79)

**Author Location** p17

**Epitope** GSEELRSLY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Donor MHC** A1A1, B55, B8, Cw3, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence had dramatic changes, the epitope GSEELRSly peptide was GtegiKSLh, and so likely not the actual reactive epitope in the larger peptide.

**HXB2 Location** p17 (71–85)

**Author Location** p17 (71–85 SF2)

**Epitope** GSEELRSlyNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A1, A11, B8, B27.

**HXB2 Location** p17 (71–85)

**Author Location** p17 (71–85 HXB2)

**Epitope** GSEELRSlyNTVATL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 were chronically infected and treated; 22 started treatment during acute infection; 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.

- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.

- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p17 (71–90)

**Author Location** Gag (HXB2)

**Epitope** GSEELRSlyNTVATLYCVHQ

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** assay standardization/improvement, HAART, ART

**References** Chitnis *et al.* 2003

- 17 perinatally HIV-1 infected children (0.08–16 years) were evaluated for HLA-A2-restricted IFN-gamma CD8+ CTL responses against 4 immunodominant peptides that carry HLA-A2 epitopes. Two peptides were from gp120 (one at position 112, one from the V3 loop), and one each was from gp41 and Gag. 15/17 patients responded to the Gag peptide, 13/17 to the gp41 and the non-V3 gp120 peptides, and 11/17 responded to the V3 loop. 4 children recognized all 4 peptides.
- In 10/14 children, addition of exogenous IL-15 induced increased frequencies of SFCs to the Gag peptide. IL-2 and IL-7 did not increase SFCs, however IL-2, IL-7 and IL 15 could all increase the intensity of the spots in some patients. In 4 children, IL-15 addition brought the SFC response up to the level of detection.

**HXB2 Location** p17 (73–82)

**Author Location** p17 (73–82)

**Epitope** EELRSlyNTV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4006)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope EELRSlyNTV is conserved across all clades.

**HXB2 Location** p17 (74–82)  
**Author Location** p17 (74–82 B1 and B2)  
**Epitope** ELRSLYNTV  
**Subtype** B, CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A03, A32, B08, B62, Cw3)  
**Country** Netherlands  
**Assay type** Other  
**Keywords** subtype comparisons, computational epitope prediction, superinfection  
**References** Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01\_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-B08 restricted epitope, ELkSLYNTV, varied to ELRSLYNTV in 50% of viruses in B1 within 4 years, ELkSLfNTV in 67% of viruses in strain B2 within 3 years, and ELkSLYNTV in AE at the earliest time point taken, with no changes over time. A reversion was seen in B2 to ELkSLYNTV i.e. f to Y, suggesting a lack of CTL pressure on this sequence.

**HXB2 Location** p17 (74–82)  
**Author Location** Gag (74–82)  
**Epitope** ELRSLYNTV  
**Epitope name** EV9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*08)  
**Donor MHC** A\*01, A\*02  
**Country** United States  
**Assay type** Intracellular cytokine staining, Other  
**Keywords** rate of progression, escape, immune evasion  
**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naïve subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- No CTL responses were detected against the EV9 epitope, ELRSLYNTV. A V82I variant, ELRSLYNTi was found.

**HXB2 Location** p17 (74–82)  
**Author Location** p17

**Epitope** ELRSLYNTV  
**Immunogen**  
**Species (MHC)** human (B\*0801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008  
 • Noted by Brander to be a B\*0801 epitope.

**HXB2 Location** p17 (74–82)  
**Author Location** p17  
**Epitope** ELRSLYNTV  
**Immunogen**  
**Species (MHC)** human (B8)  
**References** Goulder *et al.* 1997g  
 • Defined in a study of the B8 binding motif.

**HXB2 Location** p17 (74–82)  
**Author Location** p17 (74–82)  
**Epitope** ELRSLYNTV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Birk *et al.* 1998b  
 • A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

**HXB2 Location** p17 (74–82)  
**Author Location** p17 (74–82)  
**Epitope** ELRSLYNTV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Ferrari *et al.* 2000  
 • One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p17 (74–82)  
**Author Location** p17 (74–82)  
**Epitope** ELRSLYNTV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Day *et al.* 2001  
 • B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

**HXB2 Location** p17 (74–82)  
**Author Location** (B consensus)  
**Epitope** ELRSLYNTV  
**Epitope name** EV9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Donor MHC** A11, A29, B08, B44, Cw4, Cw7  
**Country** United States  
**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells  
**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** p17 (74–82)

**Author Location** p17

**Epitope** ELRSLYNTV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A1A1, B55, B8, Cw3, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence ELRSLYNTV had dramatic changes, the epitope peptide was gikSLhNTV, and so likely not the actual reactive epitope in the larger peptide.

**HXB2 Location** p17 (74–82)

**Author Location**

**Epitope** ELRSLYNTV

**Immunogen**

**Species (MHC)** (B8)

**Keywords** review, immunodominance, escape, vaccine antigen design

**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

**HXB2 Location** p17 (74–83)

**Author Location** Gag

**Epitope** ELRSLYNTVA

**Epitope name** 1241

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for ELRSLYNTVA: 71%. This epitope was previously identified in the literature, but was not confirmed in this study.

**HXB2 Location** p17 (76–86)

**Author Location** p17 (76–86)

**Epitope** RSLYNTVATLY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*30)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, subtype comparisons, acute/early infection

**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, RSLYNTVATLY, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences.

**HXB2 Location** p17 (76–86)

**Author Location** p17 (74–86 LAI)

**Epitope** RSLYNTVATLY

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*3002)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*3002 epitope.

**HXB2 Location** p17 (76–86)

**Author Location** p17 (SF2)

**Epitope** RSLYNTVATLY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Keywords** subtype comparisons, immunodominance



**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a single HIV+ individual from Boston – this epitope fell outside the most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNMLNTVG (p24 41-60), and WEKIRL-RPGGKKKYK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKPEFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p17 (76–86)**Author Location** Gag (96ZM651.8)**Epitope** RLSYNTVATLY**Immunogen****Species (MHC)** human (A\*3002)**References** Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- Only 3/13 (23.1%) A\*3002-positive subjects demonstrated moderate CTL responses to the peptide GTEELRSLYNTVATLYCVHE (residues 71 to 90), which contains the previously described A\*3002 epitope RLSYNTVATLY.

**HXB2 Location** p17 (76–86)**Author Location** p17 (76–86)**Epitope** RLSYNTVATLY**Epitope name** RY11 (p17)**Immunogen** HIV-1 infection**Species (MHC)** human (A\*3002)**References** Goulder *et al.* 2001a

- HLA-A\*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule.
- A rapid method was developed combining ELISPOT with intracellular IFN- $\gamma$  staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood.
- Two individuals were studied: Subject 199 (HLA A\*0201/\*3002 B\*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A\*3002/ B53/\*5801 Cw4/7) an African-Caribbean.
- In both HLA-A\*3002 individuals the response to RSLYNTVATLY was dominant.
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41).
- HLA-A\*3001-positive targets do not present RSLYNTVATLY.

**HXB2 Location** p17 (76–86)**Author Location****Epitope** RLSYNTVATLY**Epitope name** Gag-RY11**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*3002)**Donor MHC** A\*3002, A\*3201, B\*4501, B\*5301, Cw\*0401, Cw\*1202**Keywords** HAART, ART**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 00RCH33 was on HAART had a viral load of 2900 and CD4 count of 727 and also recognized the epitopes YPLTFGWY, Nef(135-143), HLA B\*5301; AETFYVDGA, RT(437-445), HLA B\*4501; and HIGPGRAFY, gp160(310-318), HLA A\*3002.
- Among HIV+ individuals who carried HLA B30, 3/16 (19%) recognized this epitope.

**HXB2 Location** p17 (76–86)**Author Location** (C consensus)**Epitope** RLSYNTVATLY**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*3002)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** characterizing CD8+ T cells**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p17 (76–86)**Author Location** (C consensus)**Epitope** RLSYNTVATLY**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*3002)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RSLYNTVATLY is an optimal epitope.

**HXB2 Location** p17 (76–86)

**Author Location** p17 (74–86 SF2)

**Epitope** RSLYNTVATLY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A30)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A30+ individuals that had a CTL response to this epitope broken down by group: 0/1 group 1, 0/0 group 2, and 1/1 group 3.

**HXB2 Location** p17 (76–86)

**Author Location** p17

**Epitope** RSLYNTVATLY

**Epitope name** A30-RY11(p17)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A30)

**Donor MHC** A30, A32, B18, B27

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8+ T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.

- Treatment interruption following HAART resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient D displayed the greatest response to B27-KK10 (p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

**HXB2 Location** p17 (76–86)

**Author Location** p17

**Epitope** RSLYNTVATLY

**Epitope name** RY-11

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A30)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA

**References** Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized.
- RSLYNTVATLY was presented by A\*30, which is more common in Zulus than Caucasians (0.195 versus 0.019). This epitope had previously identified in B clade infections.

**HXB2 Location** p17 (76–86)

**Author Location** p17

**Epitope** RSLYNTATLY

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A30)

**Donor MHC** A\*02, A\*30, B\*15, B\*4402

**Assay type** T-cell Elispot

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 4/8 HIV epitopes tested in an IFN $\gamma$  Elispot assay or tetramer assay. Responses were detected 8 and 28 weeks after exposure, this particular epitope was only tested with Elispot.

**HXB2 Location** p17 (76–86)

**Author Location**

**Epitope** RSLYNTVATLY

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (A30)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p17 (76–86)

**Author Location**

**Epitope** RSLYNTVATLY

**Immunogen**

**Species (MHC)** human (B58)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B58 epitope.

**HXB2 Location** p17 (76–86)

**Author Location**

**Epitope** RSLYNTVATLY

**Immunogen**

**Species (MHC)** human (B63)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B63 epitope.

**HXB2 Location** p17 (76–86)

**Author Location** p17

**Epitope** RSLYNTVATLY

**Epitope name** RY11

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B58, B63)

**Donor MHC** A\*02, A\*24, B\*1517, B\*58, Cw\*03, Cw\*07

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.

- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. Peptide reactivity was enriched for those that carry B63, with a trend for those that carry B57/B58. Optimal epitope was defined in an individual that was B\*1517(B63)/B58 positive.

**HXB2 Location** p17 (76–88)

**Author Location** Gag (76–84 SIV)

**Epitope** KSLYNTVCV

**Epitope name** KV9

**Immunogen** vaccine

*Vector/Type:* DNA, DNA prime with virus-like particle (VLP) boost *Strain:* SIV *HIV component:* Gag

**Species (MHC)** mouse (H2-Db)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining

**Keywords** vaccine-induced epitopes, immunodominance, vaccine antigen design, SIV

**References** Liu *et al.* 2006a

- An SIV Gag DNA vaccine was studied in mice in order to enhance subdominant immune responses to the KV9 epitope, without compromising its immunodominant response to the Gag AL11 epitope. Both epitopes share a common MHC restricting allele. Novel vaccine strategies including anatomic separation and heterologous prime-boost were investigated to expand vaccine-elicited CTL responses. This was the first study of its kind using DNA gene-based vaccines.
- This epitope, KSLYNTVCV (KV9), was the subdominant epitope studied, but it was capable of eliciting a response of comparable magnitude to the immunodominant epitope, AL11, in the absence of AL11 during vaccine priming.
- This subdominant epitope KV9 had an augmented response even in the presence of immunodominant AL11, making their responses codominant, when vaccine administration used anatomic separation or heterologous boost strategies.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Keywords** HAART, ART

**References** Huang *et al.* 2000

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed.
- Increases in gamma IFN producing cells were observed in response to anti-retroviral therapy using single cell IFN-gamma-production ELISPOT.
- 4/8 A\*02 subjects had a positive response to this epitope indicating that it is a major epitope for CD8+ gamma IFN production.
- In 3/3 HLA A\*02, B\*27 individuals, the dominant response in gag measured by both gamma IFN production and T-cell lysis was a B27 epitope, p24(263-272), not the A2 SLYNTVATL epitope.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Keywords** HAART, ART

**References** Rinaldo *et al.* 2000

- Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that can persist after therapy and long periods of virus being below the level of detection.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Keywords** HAART, ART, immunodominance

**References** Scott-Algara *et al.* 2001

- This study examined with CTL response in HLA A\*02+ children by tetramer staining for HLA-A2 immunodominant epitopes SLYNTVATL and ILKEPVHGV.
- 71% of the 28 HIV-1 infected HLA-A\*02 positive children recognized both epitopes, with cells from 26 children stained positive by the gag tetramer (SLYNTVATL) and 21 children by the pol tetramer (ILKEPVHGV)
- There were no differences observed in children that had therapy versus those that did not.
- Tetramer-binding cells were memory activated CD28-, CD45RO+, CD45RA- HLADR+, CD69-, CD8+ T-cells.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Epitope name** GAG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** France

**Assay type** Cytokine production, Tetramer binding, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** responses in children, characterizing CD8+ T cells

**References** Scott-Algara *et al.* 2005

- Only a fraction of HIV-1-specific CD8 T-cells detected in the PBMC of 17 infected children (ages 2-18) were able to produce cytokines (IFN-gamma, TNF-alpha) or chemokines (CCL4, CCL5) after stimulation with the cognate peptide. A negative correlation was found between the plasma viral load and the percentage of CD8+ Gag-specific T-cells secreting IFN-gamma. Tetramers used in this study were SLYNTVATL-HLA-A\*02 and ILKEPVHGV-HLA-A\*02.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, subtype comparisons, acute/early infection

**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, SLYNTVATL, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- The major p17 Gag SL9 epitope, SLYNTVATL, varied to SLYNTiATL with change V82I at position 6 and SLfNTiATL with an additional change Y79F at position 3. The 79F mutant elicited lower magnitude and functional avidity responses than 82I and 79F82I mutants. Even so, in time most variants were Y79F which showed positive selection. This Y79F mutant was seen combined with upstream changes E62G/V/A. In combination with 62E and 62G however, the Y79F mutant did

not propagate successfully. Later, in combination with 62A the 79F mutant coincided with increasing viral load.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Assay type** CTL suppression of replication

**Keywords** class I down-regulation by Nef

**References** Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein Gag epitope SLYNTVATL-recognizing CTLs were affected by Nef.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection, in vitro stimulation or selection

**Species (MHC)** human (A\*02)

**Assay type** Other

**Keywords** kinetics

**References** Wick *et al.* 2005

- Experimental and mathematical models were used to estimate the number of HIV-infected cells that can be killed by CD8+ T-cells. On average, CTLs can kill from 0.7 to 3.0 cells/day.
- CTL clone 18030D23 recognizes epitope SLYNTVATL and was used to study the inhibition of HIV-1 replication in acutely infected cells in vitro.

**HXB2 Location** p17 (77–85)

**Author Location**

**Epitope** SLYNTVATL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** characterizing CD8+ T cells

**References** Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.

- A\*02-restricted epitope SLYNTVATL does not correlate with any particular CTL maturation phenotype.

**HXB2 Location** p17 (77–85)

**Author Location** Gag

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Donor MHC** A\*02, A\*03, B\*35, B\*51

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** rate of progression, acute/early infection, memory cells

**References** Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope SL9, SLYNTVATL, a patient with oscillating ART had IFN-gamma secretion by CD127 lo cells during viremia and CD127hi cell-IFN-gamma production during viremic control. Shortly after ART cessation, CD127 mixed cells secreted IFN-gamma.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Subtype** A, C, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02, A\*68)

**Country** Tanzania

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, immunodominance

**References** Geldmacher *et al.* 2007a

- To assess whether T-cell specific responses to Gag and Nef are biased towards infecting subtype recombination, 56 ART-naive subjects were studied using six overlapping peptide sets consisting 15-mer peptides, covering both proteins completely. A multi-region hybridization assay was employed. Overall, the best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants SLYNTvATL and SLfNTiATL were studied as peptide sequences SLYNTvATL-YCVHEK (subtypes C, A, D), SLfNTiATL-YCVHEK and SLfNTiATL-WCVHQR with 18% responders. Subtype C epitopes were best recognized.

**HXB2 Location** p17 (77–85)

**Author Location**

**Epitope** SLYNTVATL

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02, B\*1503)

**Assay type** Other

**Keywords** review, epitope processing, rate of progression, escape, immune evasion, viral fitness and reversion, optimal epitope, HLA associated polymorphism, compensatory mutation

**References** Blankson *et al.* 2006

- Based on two papers, Iversen 2006 and Frahm 2006, the authors point out that in choosing epitopes for use in AIDS vaccines not only immunogenicity but fitness cost of escape mutations must be considered. Thus immunization may be made to both wild-type and common escape variants. Also, while epitopes that lack sequence variation may form good targets, so would subdominant epitopes.
- Iversen *et al.* found 2 pathways of conservative residue change that affect CTL epitope contacts with HLA-A\*02 - one acquiring escape mutations (SLfNTiAvL) and the other retaining or reverting to index residues in Gag protein's SLYNTVATL (SL9) epitope.
- Since viral loads in patients with escape mutations in SL9 are typically lower, it is suggested that CTL responses to subdominant epitopes in such patients may be involved in replication control. Frahm *et al.* showed subdominant epitopes of an HLA-B\*1503 restricted response to HIV were able to reduce viremia.

**HXB2 Location** p17 (77–85)

**Author Location** (LAI)

**Epitope** SLYNTVATL

**Epitope name** S9L

**Subtype** B

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other

**Species (MHC)** human, transgenic mouse (A\*02.01)

**Country** France

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other

**Keywords** computational epitope prediction, Th1

**References** Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors *in vitro*.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.
- Epitope S9L was one of 2 CTL reporter epitopes in recombinant mouse invariant chain constructs used for readout in a penatmer staining assay.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 HXB2)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** epitope processing, immunodominance, escape

**References** Brander *et al.* 1999

- Multiple natural variations in the SL9 flanking regions of the immunodominant epitope SLYNTVATL were tested and found not to adversely affect CTL recognition or prevent epitope processing, suggesting that viral escape from the HLA-A\*0201-restricted CTL response against SLYNTVATL is probably not linked to variations in the flanking regions of this epitope.
- The substitution Y79F was an escape mutation in that it interfered with CTL recognition by one CTL clone from an A\*0201 infected individual, clone 13010.B17, but it was still recognized by another CTL clone, 115.D4.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** acute/early infection

**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T-cells and viral load was also found.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWIIIGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** p17 (77–85)

**Author Location** Gag

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Tan *et al.* 1999

- Adoptive transfer of two autologous *in vitro*-expanded CTL clones against the A\*0201 restricted epitopes SLYNTVATL and VIYQYMDDL were infused into a patient – they were well tolerated, but the SLYNTVATL clone was shown by tetramer staining to be rapidly eliminated through apoptosis, and the treatment had no impact upon viral load and CD4 and CD8 cell counts.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- Individuals who did not respond to SLYNTVATL recognized other HIV epitopes, and 2/4 SLYNTVATL responders had stronger responses to epitopes restricted by other class I alleles.
- SLYNTVATL was the only response detected in a one individual that was HLA A\*0201, B44, B70.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** HAART, ART

**References** Ogg *et al.* 1999

- CTL effector levels were measured after potent ARV therapy using HLA-tetramer complexes for the A\*0201 epitopes SLYNTVATL and ILKEPVHGV in seven patients, and the B\*3501 epitope DPNPQEVVL in one additional patient.
- Levels of CTL effectors typically decline for 5-7 days and then rebound, fluctuating during the first two weeks of therapy.
- After the early fluctuation, there was a steady exponential decay with a median half-life of 45 days.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Altman *et al.* 1996

- This paper introduces the tetramer methodology that permits quantification of specific CTL based on expression of specific TCRs – HLA-A2 tetramers were prepared that can stain CTL lines specific for ILKEPVHGV and SLYNTVATL, and quantitate HIV-specific CD8+ cell lines in freshly isolated PBMCs.
- Three patients only stained the Gag epitope SLYNTVATL, one patient had the highest frequency of tetramer staining to the Pol epitope (0.77%), less to the Gag epitope (0.28%).

**HXB2 Location** p17 (77–85)

**Author Location** Gag

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** HAART, ART

**References** Gray *et al.* 1999

- Administration of highly active antiretroviral therapy (HAART) reduced CD8+ cell frequency, and the CD8+ cells detected by tetramer staining were likely to be memory cells, indicating that persistently replicating viral populations are needed to maintain high frequencies of HIV-1 specific CTL.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 SF2)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** subtype comparisons

**References** McAdam *et al.* 1998

- CTL from a patient infected with clade B virus did not recognize the clade A analog of this epitope.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** TCR usage

**References** Wilson *et al.* 1998a

- HIV+ individuals were followed longitudinally using MHC tetramers in combination with 14 anti-BV chain MAbs, and clonal expansion of HIV-specific T cells was followed *in vivo*.
- Seven HIV+ people were studied, and all showed expansions of particular TCR BV clones, often several, relative to uninfected controls.
- Three patients were followed in detail, TCR VB expansions persisted for 2 to 3 years, with occasional transient increases.
- An A2-Gag specific line from one patient was found to be BV8, and at its highest level represented 17.5% of the patient's CD8+ T cells.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Ogg *et al.* 1998b

- HLA-tetrameric complexes were used in a cross-sectional study of 14 untreated HLA A\*0201 positive individuals, revealing an inverse relationship between HIV Gag and Pol specific CTL effector cells (CTL<sub>e</sub>) and viral load.
- Inclusion of both the p17 SLYNTVATL and RT ILKEPVHGV epitopes gives a good representation of HLA A\*0201-restricted activity.
- No correlation was observed between the CTL<sub>e</sub> and CD4 count or clearance rate of productively infected cells.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (A\*0201)  
**Keywords** epitope processing  
**References** Walter *et al.* 1997

- HLA-A2 heavy chain and  $\beta$ 2-microglobulin expressed in *E. coli* were refolded in the presence of this peptide.
- The HLA-A2-peptide complex elicited HLA-A2 peptide-specific CTL response in cells lacking HLA-A2.
- Suggests that preformed HLA-peptide complexes could provide an alternate to intracellular processing for immunogens.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**References** Lalvani *et al.* 1997

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers.
- This peptide was one of the test peptides for optimizing the protocol.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (76–84)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (A\*0201)  
**References** van der Burg *et al.* 1996

- Slow dissociation rate is associated with immunogenicity.
- CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** review, escape  
**References** Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical siblings, hemophiliac brothers, were both infected with the same batch of factor VIII.
- One had a response to gag A2 epitope SLYNTVATL, the other to pol A2 epitope ILKEPVHGV. They were tested 6-8 years after infection.
- Viral sequencing from the twin that had no response to SLYNTVATL indicated his virus had the substituted form SL-HNAVAVL.
- 71% of an additional set of 22 HIV-1 infected HLA-A\*0201 positive donors preferentially responded to gag SLYNTVATL.

- Those individuals with a pol ILKEPVHGV response tended to have mutations in or around SLYNTVATL.
- An additional subject went from SLYNTVATL responder to non-responder coincident with a switch to the variant SLFNTVATL.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** review  
**References** Goulder *et al.* 1997a

- This paper is a review of CTL and immune evasion, but it presents a study of a shift from an HLA-A\*0201 response to SLYNTVATL, to a B62 response to GLNKIVRMY.
- As long as a strong CTL response to SLYNTVATL was evident, the epitope variants SLFNTVATL or SLYNTIATL dominated the viral population – eventually the CTL response to the index peptide became undetectable, the CTL response shifted to a focus on GLNKIVRMY, and the index peptide SLYNTVATL once again established itself as the dominant form.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** HAART, ART  
**References** Gray *et al.* 1999

- Peptide-tetramer complexes of A\*0201 and SLYNTVATL or ILKEPVHGV were used to study individuals receiving HAART to determine the frequency of Class I HLA-restricted anti-HIV CD8+ T cells.
- 17/18 asymptomatic patients had a CTL response to one or both epitopes – 72% had a CTL response to SLYNTVATL.
- After HAART, the majority of the epitope-specific CTL were apparently memory cells.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85 subtype A)  
**Epitope** SLFNTVATL  
**Epitope name** SL9  
**Subtype** A  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** subtype comparisons  
**References** Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, two with subtype A infections, one with subtype C – their infections all originated in East Africa.
- This epitope is most commonly SLYNTVATL in B subtype, and CTL from the C subtype infection did not recognize B clade gag or the 3Y form of the epitope, but did recognize the predominant A and C clade form, SLFNTVATL.



**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** immunodominance

**References** Brander *et al.* 1998a

- Of 17 infected HLA A\*0201 subjects, 13 had CTL responses against the p17 SLYNTVATL epitope, six recognized ILKEPVHGV and five recognized VIYQYMDDL, and there was no correlation between viral load and recognition of a specific epitope.
- Only one subject had CTL against all three epitopes.
- There was significant heterogeneity in the CTL response to this immunodominant epitope.
- The overall variation in this epitope among the 17 who had a CTL response and 11 non-HLA A\*0201 HIV-1 + individuals was similar, suggesting a lack of immune pressure.
- Subjects were part of the San Francisco City Clinic Cohort, the ARIEL project and from the Boston area.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 HXB2)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** rate of progression, immunodominance

**References** Hay *et al.* 1999

- CTL response to IPRRIRQGL was the immunodominant response in a rapid progressor – there was a subdominant response to SPAIFQSSM in Pol, and interestingly, no response to commonly immunodominant HLA A\*0201 epitope SLYNTVATL, although this individual was HLA A\*0201.
- The individual showed a strong initial CTL response at the time of the initial drop in viremia, but it was quickly lost, although memory cells persisted.
- Despite the initial narrow response to two epitopes, no other CTL responses developed.
- No HIV-specific lymphoproliferative responses were detected in this patient, and neutralizing antibody response was weak.
- A variant of this epitope was observed *in vivo* (–F—V–), but this mutation is recognized by SLYNTVATL-specific CTL, and in this case the patient's cells could present the peptide to SLYNTVATL-specific CTL.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** HAART, ART

**References** Kalams *et al.* 1999b

- Two patients were followed before and after HAART – reduced plasma HIV-1 RNA levels resulted in a decline in HIV-specific *in-vivo* activated CTL such that by day 260 CTL activities were undetectable.

- ERYLKDQQL was the dominant response in one of the individuals, SLYNTVATL subdominant.
- Sporadic breakthrough in viremia resulted in transient increases in CTLp.
- Memory CTL frequency directed against Vac-Gag, Vac-RT, Vac-Env, and Vac-Nef initially increased with HAART and then decreased with the decline of the viral load.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Spiegel *et al.* 2000

- High levels of CD8+ HIV-1 specific and cytomegalovirus specific CTL were detected by HLA-A\*0201-peptide tetramers in 3 infected subjects with very low CD4 counts, but CD8 T cell mediated effector activity was not seen.
- Thus HIV-1 specific CD8+ cells may be present but may lack direct effector activity in late disease, suggesting that overcoming antigen unresponsiveness may be a useful therapeutic strategy.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Larsson *et al.* 1999

- ELISPOT was used to assay the CD8+ T-cell response to the HIV-1 proteins Gag, Pol, Nef or Env expressed in vaccinia vectors in 19 HIV+ people.
- The highest CTL frequency was directed at epitopes Pol.
- In A\*0201 individuals, higher numbers of spot-forming T cells were directed against HIV-1 proteins expressed in vaccinia than to peptides SLYNTVATL and ILKEPVHGV presented by A2.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (SF2)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in 11/25 HLA A2 (A\*0201 or A\*0202) HIV+ individuals from Boston and in 1/8 HLA A2 HIV+ individuals from Durban.
- Three peptides GSEELRSLYNTVATL (p17 residues 71–85), SALSEGATPQDLNMLNTVG (p24 41–60), and WEKIRL-RPGGKKKYKLLK (p17 16–30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20–36), ELRSLYNTVATLYCV (p17Gag 74–88), SALSEGATPQDLNMLNTVG (p24 41–60), FRDYVDRFFKTLRAEQA (p24 161–177), and SILDIKQGKEPFRDY (p24 149–164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85 LAI)  
**Epitope** SLYNTVATL  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (A\*0201)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008  
 • C. Brander notes this is an A\*0201 epitope.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85 SF2)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** escape, acute/early infection  
**References** Goulder *et al.* 2001a

- This epitope is targeted by 75% of HLA-A\*0201, HIV+ adults, and the magnitude of the response is inversely correlated with viral load.
- CTL responses to SL9 and autologous SL9 variants were not detected in 11 HLA-A\*0201 positive subjects during acute infection.
- Longitudinal studies of two individuals (AC13 and PI004) showed that the initial control of viremia was independent of the SL9 CTL response.
- Low Gag expression levels did not correlate with the delayed CTL response to this epitope.
- Autologous SL9 variants SLYNTI AVL, SLYNTV AVL, SLFNTVATL, SLFNTVATL, and SLFNTVATL are each capable of inducing a range of CTL responses, sometimes strong, sometimes diminished, and sometimes complete escape relative to the wild type variant SLYNTVATL in patients with chronic HIV-1 infection – the ability to cross-react with a particular variant was patient dependent.

**HXB2 Location** p17 (77–85)  
**Author Location** p17  
**Epitope** SLYNTVATL  
**Epitope name** p17 SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** subtype comparisons, supertype, computational epitope prediction  
**References** Altfeld *et al.* 2001c  
 • HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.  
 • Three additional previously described HLA-A2 epitopes were added to the set of 20, including p17 SL9, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2).  
 • p17 SL9 was recognized in 12/22 patients with chronic HIV-1 infection.

- Only 1/13 patients with acute HIV-1 infection recognized p17 SL9.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag  
**Epitope** SLYNTVATL  
**Epitope name** (SL9)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**References** Goepfert *et al.* 2000

- This paper describes a comparison of results of different CTL assays, a SL9 tetramer assay and IFN-gamma ELISPOT, using 7 HIV-positive patients.
- The IFN-gamma ELISPOT assay was compared using the single SL9, a pool of overlapping 20 mers, and recombinant vaccinia encoding Gag as antigen – pooled peptides gave the highest number of spot forming cells, vaccinia gave high background.
- A correlation with results of the tetramer assay was found only for ELISPOT using the Gag epitope as antigen, but the tetramer assay detected a 10-fold higher number of cells than could produce IFN-gamma in the ELISPOT assay – the authors suggest not all tetramer-positive cells may produce IFN-gamma, some may be undergoing apoptosis, some may be producing other cytokines.
- The tetramer assay could detect a reaction to SLYNTVATL in most of the HLA-A\*0201 chronically HIV-1 infected study subjects.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag (77–85)  
**Epitope** SLYNTVATL  
**Immunogen**  
**Species (MHC)** human (A\*0201)  
**Keywords** binding affinity  
**References** Sandberg *et al.* 2000

- This epitope served as a positive control in a study comparing peptide binding affinity to HLA-A201 to CTL responses upon vaccination with a nef DNA vaccine.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag (LAI)  
**Epitope** SLYNTVATL  
**Subtype** B  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (A\*0201)  
**Keywords** dendritic cells  
**References** Engelmayr *et al.* 2001

- Recombinant canarypox virus vector containing HIV-1 sequences, upon infection of mature dendritic cells, can trigger specific lysis through *in vitro* by T-cells from HIV-1 infected individuals at levels comparable to the response seen to HIV carried in vaccinia vectors.
- Recombinant canarypox virus vector containing HIV-1 sequences can also stimulate HIV-specific CD4+ helper T-cell responses.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85 LAI)  
**Epitope** SLYNTVATL

- Epitope name** G3  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** HAART, ART  
**References** Mollet *et al.* 2000
- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using tetramer staining or CD8+ cell IFN $\gamma$  production to measure responses.
  - In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
  - Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

- HXB2 Location** p17 (77–85)  
**Author Location** Gag  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**References** Gea-Banacloche *et al.* 2000
- In a study including many long-term non-progressors, no correlation between plasma virus levels and number of HIV-specific CD8+ T-cells was found.
  - High frequencies of circulating CD8+ T-cells were HIV-1 specific, and the majority of these responses were to gag-pol gene products.
  - 4/21 subjects were HLA-(A\*0201), and of these only 2 subjects (patient 3 and 19) tested positive to this epitope.

- HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85 SF2)  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** supertype, rate of progression  
**References** Propato *et al.* 2001
- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
  - Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
  - A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
  - Tetramer staining with A2, beta2microglobulin, and either SLYNTVATL, KLVGKLNWA, or LTFGWCFKL revealed that tetramers detected more HIV-specific sells in LTNP than in progressors, activated effector cells were the minority population, and ELISPOT correlated better with the effector cell subpopulation than the total tetramer stained population.

- HXB2 Location** p17 (77–85)  
**Author Location** Gag (77–85)  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** HAART, ART, rate of progression  
**References** Jin *et al.* 2000a
- The CTL effector levels (CTLe) were compared in long term non-progressors (LTNP) with low viral load and in patients whose virus was well-suppressed by therapy, using a tetramer assay.
  - LTNPs have high memory CTLe numbers and low viral load, while HAART patients had low CTLe numbers and low viral load.

- HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**References** Appay *et al.* 2000
- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
  - HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
  - In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$ .

- HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**References** Goulder *et al.* 2000b
- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA]).
  - HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection.

- HXB2 Location** p17 (77–85)  
**Author Location** p17  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** dendritic cells  
**References** Ostrowski *et al.* 2000
- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*.
  - Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T cell help in 9/10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T cell help to a variable degree in most of patients.

- Those CTL that didn't respond to CD40LT could expand with IL2 present, and IL15 produced by dendritic cells also contributes.
- The T-helper epitope used for CD4+ T cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKAN-SKFIGITE).

**HXB2 Location** p17 (77–85)

**Author Location**

**Epitope** SLYNTVATL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* canarypox prime with gp120 boost, canarypox prime with gp160 boost  
*Strain:* B clade LAI, B clade MN, B clade SF2  
*HIV component:* Gag, gp120, gp41, Nef, Pol

**Species (MHC)** human (A\*0201)

**Keywords** vaccine-specific epitope characteristics

**References** Ferrari *et al.* 2001

- Different HIV strains were used for different regions: gp41 LAI, Gag LAI, gp120 MN, gp120 SF2.
- Two vaccinees with Gag responses were HLA-A\*0201+, but neither made SLYNTVATL responses to the Gag vaccine, in contrast to its frequent recognition in natural infections. No HLA-A\*0201 responses were observed to an Env vaccine.

**HXB2 Location** p17 (77–85)

**Author Location**

**Epitope** SLYNTVATL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** rate of progression, immunodominance

**References** Migueles & Connors 2001

- CTL activity was monitored in 27 individuals, including 10 LTNP with an over-expression of HLA B\*5701 – these individuals have viral loads below the threshold of infection without therapy, and their immune response tends to be focused on peptides that contain B\*5701 epitopes ISPRTLNAW, KAF-SPEVIPMF, TSTLQEIQIGW, and QASQEVKNW.
- CTL responses are broader in B\*5701+ individuals with progressive viremia than those that control viremia.
- The HLA-A\*0201 SLYNTVATL epitope response was not as strong in individuals that carried both A2 and B57.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** epitope processing, immunodominance

**References** Sewell *et al.* 2002

- Epitope processing of three different HLA-A\*0201 HIV epitopes was shown to use different pathways, which might influence patterns of immunodominance. 174 cells were used that lack TAP1 and TAP2 genes, as well as the LMP2 and

LMP7 genes that encode the beta-subunits of the immunoproteasome. These genes could be added back through transfection to study processing.

- ILKEPVHGV was efficiently presented in TAP-1 and -2 transfected cells while VIYQYMDDL and SLYNTVATL were not. VIYQYMDDL was destroyed by the MB1 subunit of the protease, and could be expressed in the presence of the proteasome inhibitor lactacystin, but SLYNTVATL expression was not restored. SLYNTVATL expression was unaltered by lactacystin in a wild type cell line.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (ADA)

**Epitope** SLYNTVATL

**Epitope name** SL-9

**Subtype** B

**Immunogen** HIV-1 infected monocyte-derived

**Species (MHC)** mouse (A\*0201)

**References** Poluektova *et al.* 2002

- Nonobese diabetic NOD-C.B-17 SCID mice were reconstituted with HLA-A\*0201 positive human PBL and injected with HIV-1 infected monocyte-derived macrophages MDM in the basal ganglia to provide a mouse model of HIV-1 encephalitis.
- HLA-A\*0201 CTL responses were detected by tetramer staining in the spleen in seven days, increased through day 14, and the numbers of productively infected were reduced >85% in the second week.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 LAI)

**Epitope** SLYNTVATL

**Epitope name** LR23

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide  
*Strain:* B clade LAI  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG

**Species (MHC)** mouse (A\*0201)

**Keywords** binding affinity, vaccine-specific epitope characteristics, immunodominance

**References** Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRFVTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a strong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85 LAI)  
**Epitope** SLYNTVATL  
**Epitope name** LR23  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade LAI  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12, P30  
**Species (MHC)** mouse (A\*0201)  
**Keywords** vaccine-specific epitope characteristics, immunodominance  
**References** Peter *et al.* 2002

- When HIV-1 peptides were used to vaccinate HLA-A2.1 transgenic A2-Kb mice, strong responses to five peptides were observed when the peptides were given individually, but immunodominance limited the response to some of the peptides when they were given in combination Peter *et al.* [2001]. IL-12 can counteract immunodominance in BALB/c mice, so it was given with the multiple epitope vaccination, and was instead found to specifically eliminate the HLA-A2.1-epitope CTL responses, but not Kb CTL responses. This was possibly a consequence of transient depletion of T-cells, B cells and macrophages in the spleen.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Immunogen** computer prediction  
**Species (MHC)** (A\*0201)  
**Keywords** subtype comparisons, computational epitope prediction, vaccine-specific epitope characteristics, escape  
**References** Schönbach *et al.* 2002

- Computational methods (artificial neural networks [ANN], hidden Markov models [HMM], binding matrices based on HLA association rates BIMAS) were used to identify HLA-A\*0201 and HLA-B\*3501 HIV T-cell epitope candidates from 533 Gag, Env and Pol sequences of which 374 were derived from HIV-1, 97 were derived from HIV-2 and 62 from SIV. Comparisons to known epitopes and between clades were made.
- The SLYNTVATL epitope received focused discussion. SLYNTVATL, sIFntvatl, slyntvaVI, and slyntIaVI are all recognized variants, ANN predicts all four variants would be recognized, while BIMAS only predicts SLYNTVATL and sIFntvatl would be recognized. However, Sewell *et al.* [1997] suggested certain substitutions may be antagonistic, including sIFntvatl, and vaccines do not stimulate SLYNTVATL responses as well as natural infections. The authors note these kinds of issues complicate the application of computational predictions of epitopes to vaccine design.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag (76–84)  
**Epitope** SLYNTVATL  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* HIV-1  
**Species (MHC)** mouse (A\*0201)

**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Singh *et al.* 2002; Sykes & Johnston 1999

- C3H (H-2k) transgenic mice carrying a fused HLA-A\*0201 alpha1 and alpha2 and H-2Dk alpha3 hybrid class I molecule were immunized using an epidermal gene gun with an ubiquitin expression library of 32 plasmids that spanned the HIV-1 genome. Ubiquitin targets the expressed HIV-1 peptides to the proteasome.
- A single immunization with the UB-HIV-1 library vaccine induced potent, stable and multivalent CTL responses against all library members.
- Immunodominant epitopes SLYNTVATL (Gag), ILKEPVHGV (Pol), RIQRGPGRAFVTIGK (Env) and AFHHVAREK (Nef) elicited strong CD8+/IFN- responses and stimulated CTL that were functional in a Cr-release assay and against wild type antigen.
- The presence of multiple plasmids HLA-A\*0201-restricted CTL epitopes did not decrease CTL immunogenicity, and CTL responses to single peptide immunizations were comparable to responses based on mixtures of either 16 or 32 peptides.

**HXB2 Location** p17 (77–85)

**Author Location**

**Epitope** SLYNTVATL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Donor MHC** A\*0202, A\*2501, B\*1801, B62, Cw\*1203, Cw10, DQB1\*8, DRB1\*1501

**Keywords** rate of progression, Th1, Th2

**References** Imami *et al.* 2002b

- 70 patients with chronic disease progression, 10 clinical non-progressors, and 3 immunologically discordant progressors (individuals who controlled viremia but had progressive CD4+ T-cell decline) were analyzed for their T-helper cell responses to p24 and cytokine profile. Long term non-progressors had much stronger Th responses, particularly to p24 peptides, and they tended to be balanced between Th1, IL-2 producing and Th2, IL-4 producing responses.
- One of the immunologically discordant progressors became symptomatic during the course of the study, and he had a rapid drop in proliferative response to all antigens and also a shift from a Th1 to a Th2 response. To find out if the CD8 response also shifted in cytokine production, the CD8+ T-cell response to SLYNTVATL in this patient was also tested. It too was found to shift, from IFN $\gamma$  to IL-4 producing in Eli-spot, and using a bioassay of indicator lines, from IL-2 to IL-4 production.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Donor MHC** A\*0201, A11, B51, B61, Cw\*14, Cw2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- Only 1/10 HLA A\*02 carrying individuals in this study recognized SLYNTVATL.
- All HIV-1 proteins except Vpu were recognized, and responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** p17 (77-85)**Author Location****Epitope** SLYNTVATL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201)**Assay type** Cytokine production, proliferation, Tetramer binding, Intracellular cytokine staining, Chromium-release assay**References** Dagarag *et al.* 2003

- Telomere length is short in the CD8+ T-cell compartment of HIV-1 infected people, indicating excessive CTL activation and premature senescence. Here human telomerase RT (hTERT) transduction of HIV-1-specific CTL was used to study the functional impact of telomerase. Telomerase expression enhanced proliferative capacity, as well as cytolytic and antiviral capabilities; cytokine production was unchanged. hTERT transduced CTLs were 10-fold more efficient in controlling HIV-1 replication in culture. Thus telomerase transduction can restore CTL mediated cytolysis, and may have therapeutic potential.
- Three polyclonal CD8+ T-cell lines derived from an HIV-1, HLA A\*0201 positive patient were used in this study, including one specific for this epitope.

**HXB2 Location** p17 (77-85)**Author Location** p17 (77-85)**Epitope** SLYNTVATL**Subtype** B**Immunogen** vaccine*Vector/Type:* peptide *HIV component:* p24 Gag**Species (MHC)** mouse (A\*0201)**Donor MHC** A2.1**Assay type** Cytokine production, Chromium-release assay**Keywords** binding affinity, vaccine-induced epitopes**References** Okazaki *et al.* 2003

- Alanine substitutions of VIYQYMDDL were tested for importance of each amino acid for HLA-A2.1 binding. Peptide variant (vLyqymddV) showed an 8 fold higher MHC binding affinity than wild type. YLyqymddV had an even higher binding affinity, but the Y at position one blocked TCR recognition. The higher affinity form of vLyqymddV induced CTL *in vivo* that could protect against a vaccinia virus expressing RT and the wild type epitope.
- SLYNTVATL was included as a control.

**HXB2 Location** p17 (77-85)**Author Location** Gag (77-85)**Epitope** SLYNTVATL**Epitope name** SL9**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201)**Assay type** Tetramer binding**Keywords** genital and mucosal immunity**References** Shacklett *et al.* 2003

- Lymphocytes from rectal biopsies were used to characterize the CD8+ T cell response to HIV in GALT, Gut-associated lymphoid tissues. Patients were selected on the basis of being HLA-A2+ and having detectable SLYNTVATL and ILKEPVHGV tetramer responses in PBMC. SLYNTVATL frequency was increased in GALT relative to PBMC in 6/7 patients studied, while a control response to a CMV-peptide was diminished in GALT. Only two patients had ILKEPVHGV CD8+ T cell responses, and both had slightly higher frequencies in GALT than PBMC.
- HIV may perturb lymphocyte retention in GALT, suggested by an overall reduction of GALT CD8+ cells expressing alphaEbeta7. GALT HIV-specific CD8+ T cells expressed alphaEbeta7, suggesting mucosal priming.

**HXB2 Location** p17 (77-85)**Author Location****Epitope** SLYNTVATL**Epitope name** SL9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, T-cell Elispot, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay**Keywords** epitope processing, escape, variant cross-recognition or cross-neutralization**References** Jamieson *et al.* 2003

- Epitope escape mutations in chronically infected individuals developed over several years indicating selective advantage of escape mutants. The maturation state of CTLs appear to affect the rate of epitope mutation and CTL decay.
- In two patients, SL9-specific CTL peaked at 2-4 years post-infection; at that point the escape mutations began to dominate followed by CTL decline with a 6 month lag, suggesting CTL decline resulted as a consequence of escape. In a third patient, the initial response was 1/2 as strong and mutations did not

arise until 6-7 years post-infection; in that case the decline in SL9 CTL preceded epitope mutation.

- Two patients HLA-A\*0201 started out with a non-consensus sequence, sIFntvatl. In one of the patients, a transient reversion to the consensus was observed after 4 years, that did not reappear until the 11th year, suggesting the possibility that a reversion to the consensus form occurred, but a CTL response may have limited it so that this more fit form could not reassert itself until the patient had a more severely compromised immune response.

**HXB2 Location** p17 (77–85)

**Author Location** Gag

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A\*0201)

**Country** United States

**Assay type** Cytokine production, Tetramer binding, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** epitope processing, rate of progression, immunodominance, acute/early infection, dendritic cells, TCR usage, memory cells

**References** Kan-Mitchell *et al.* 2004

- SL9-specific CTLs were shown to be primed by immature DCs and independent of help from CD4+ or exogenous IL2, and sensitive to paracrine IL-2 induced apoptosis. The authors suggest that the reason SL9 responses are not seen during acute infection is the high level of innate immune responses resulting in cytokine-induced apoptosis, but that these CD8+ T-cells would come to dominate later infection when CD4 help is diminished.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Donor MHC** A\*0201, A\*2402, B\*52, B75, Cw\*03; A\*0201, A\*31, B\*27, B\*5101, Cw\*02; A\*0207, A\*2402, B\*46, B\*52, Cw\*01

**Country** Japan

**Assay type** Chromium-release assay

**Keywords** epitope processing, escape

**References** Yokomaku *et al.* 2004

- Epitope variants escaped from being killed by CTLs in an endogenous expression system although they were recognized when corresponding synthetic peptides were exogenously loaded onto the cells. Escape is thus probably due to changes that occur during the processing and the presentation of epitopes in infected cells.
- Endogenously expressed wild type epitope and slyntIatI variants were recognized by CTL clones while slynLvatl, sIFntvaVl and sVyntvatl variants were not. sVyntvatl and sIFntvaVl variants were, however, recognized when added exogenously to the cells.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 LAI)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* canarypox prime with gp120 boost, vaccinia prime DNA boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease *Adjuvant:* GM-CSF

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** vaccine-specific epitope characteristics, immunodominance, characterizing CD8+ T cells

**References** Ferrari *et al.* 2004

- Thirteen HLA-A\*0201 vaccines with anti-Gag CD8+ CTL reactivities were tested in uninfected HIV vaccine recipients to examine the pattern of SL9 epitope immunodominance. None of the vaccines had a detectable anti-SL9 response, in contrast to 75% of HLA A\*0201 chronically infected HIV+ individuals that respond to this epitope.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** review, rate of progression, escape, acute/early infection

**References** Goulder & Watkins 2004

- This paper is a review of the role of CTL in HIV infection, and it uses SL9 as an example of an epitope that is not responded to early in infection, yet 75% of HIV+ people respond to SL9 during chronic infection. Despite the delay in response, strong SL9 responses have been associated with lower viral loads, and escape mutations arise.

**HXB2 Location** p17 (77–85)

**Author Location** (C consensus)

**Epitope** SLYNTVATL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag (77–85)  
**Epitope** SLYNTIATL  
**Epitope name** SL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay  
**Keywords** escape, acute/early infection, characterizing CD8+ T cells  
**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this peptide was not apparent until month 20, by month 32 a T to V change was dominant, but the slyntiV1 mutant showed comparable avidity.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection, peptide-HLA interaction, vaccine  
*Vector/Type:* peptide *Strain:* multiple epitope immunogen *HIV component:* mimotopes *Adjuvant:* Incomplete Freund's Adjuvant (IFA)  
**Species (MHC)** human, transgenic mouse (A\*0201)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding  
**Keywords** vaccine-specific epitope characteristics, immunodominance, escape, TCR usage, variant cross-recognition or cross-neutralization, vaccine antigen design, mimics  
**References** Boggiano *et al.* 2005

- A combinatorial library was used to identify epitope mimics of HLA-A2 restricted CTL epitope SL9.
- 19 HIV+ HLA-A\*0201 subjects were tested for their ability to bind to peptide variants. 11/19 could bind to SLYNTVATL. Nine epitope mimics were recognized by more than a third of the subjects, and 1 subject recognized 17/20 variants tested. Some SL9 mimics were up to an order of magnitude better at stimulating CTL responses in PBMC than was SL9.

- Compared to the original SL9 sequence, some SL9 variants recognized by HLA-A\*0201 patients induced superior SL9 immune responses in HLA-A\*0201 transgenic mice.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** assay standardization/improvement, TCR usage, characterizing CD8+ T cells  
**References** Killian *et al.* 2005

- A novel technique for subtractive analysis of HIV-1 specific CTLs was developed, including depletion of peptide-specific CTLs by stimulating PBMCs with the specific peptide in the presence of 5-FU, followed by TCR spectratyping for clonal breadth analysis. In analysis of infected individuals using this technique, it was found that HIV-1 specific responses range from two to 10 different T-cell clones per epitope.
- The SL9 responses in one individual were complex, with TCR in multiple families, including: Vbeta12.2, Vbeta17, Vbeta23.3 and Vbeta22.
- This paper provides further evidence for the polyclonal nature of epitope-specific responses. Polyclonal responses may be able to better inhibit escape and may play a beneficial role in progression.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag  
**Epitope** SLYNTVATL  
**Epitope name** S9L  
**Immunogen** vaccine  
*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140 $\Delta$ V3  
**Species (MHC)** transgenic mouse (A\*0201)  
**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells  
**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** p17 (77–85)  
**Author Location** (C consensus)  
**Epitope** SLYNTVATL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)



- Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - SLYNTVATL is an optimal epitope.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** HAART, ART, responses in children, dendritic cells

**References** Zhang *et al.* 2006

- Immune responses in HIV-1 infected children either undergoing HAART or not were analysed. HIV-specific CTLs were lower in children responding to HAART than in non-responders and HAART-naive children. CTL frequency was correlated with myeloid DC frequency in treatment-naive patients, and inversely correlated with duration of virus suppression following treatment.
- 11 of the 22 children had significant responses to SL9.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.

- The best estimate of escape rate for this epitope, SLYNTVATL, was found to be 0.006/day (upper bound on rate of escape = 0.008), with SE of 0.001.
- Four variants were shown to confer escape (Y79F, Y79F-V82I, Y79F-T84V, V82I-T84V), and variant A83V was also present but untested for CTL response.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Subtype** B

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, co-receptor, characterizing CD8+ T cells

**References** Laugel *et al.* 2007a

- It was found that CD8 co-receptor differentially fine tunes CTL function via cytokine/chemokine production (MCP-1, MIP1-beta, MIP1-alpha, TNF-alpha, RANTES, IFN-gamma, IL-2 and IL-4). Differential CD8 action was controlled by abrogating its engagement using point-mutated HLA Class I molecules in 4 CTL clones specific for 3 different epitopes from HIV-1 and hTERT.
- 2 HLA-A\*0201 restricted CTL clones, SLY-10 and 003, specific for HIV-1 Gag epitope SLYNTVATL were stimulated with cognate antigen and found to have different diversities as well as hierarchies of cyto/chemokine production. Epitope variants 3H (SLHNTVATL), 3S (SLSNTVATL) and 3F (SLFNTVATL) also selectively blocked effector functions for each clone. CD8 co-receptor requirement was minimally affected for the index ligand SLYNTVATL recognition by CTL, but weaker agonists viz. the epitope variants depended more on co-receptor binding. However, MIP1-beta and IL-2 were consistently the least- and most-CD8 dependent effector secretions.
- This is the first documentation of secretion of MCP-1 by T cells. It seems to require high antigen and co-receptor dependency for release.

**HXB2 Location** p17 (77–85)

**Author Location**

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** Spain

**Assay type** Tetramer binding

**References** López *et al.* 2006

- HIV p17 sequence variability and level, phenotype and function of SL9-specific CD8+ T cells were studied in chronic patients.
- SLFNTVATL variant was found in 76% of HLA-A\*0201-positive patients and in only 25% of HLA-A\*02-negative patients.
- Patients without Tet+ cells had a significantly higher prevalence of mutations in SL9 than patients with Tet+ cells. In patients with Tet+ cells variant SLFNTVATL was associated with lower levels of Tet+ cells.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Country** Kenya  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization  
**References** Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRF-FKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequences SLYNTVATLYC and SLfNTiATL(Y/W)C are associated with HLA-A\*0201 and contain the epitope SLYNTVATL. Variable cross-reactivity was seen between subjects with respect to the 2 sequence variants.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Immunogen**  
**Species (MHC)** human (A\*0202)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes that this epitope can be presented by A\*0201 and A\*0202.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (SF2)  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0202)  
**Keywords** subtype comparisons, immunodominance  
**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in 11/25 HLA A2 (A\*0201 or A\*0202) HIV+ individuals from Boston and in 1/8 HLA A2 HIV+ individuals from Durban.
- Three peptides GSEELRSlyNTVATL (p17 residues 71–85), SALSEGATPQDLNtMLNTVG (p24 41–60), and WEKIRLRPGGKKKYKLK (p17 16–30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20–36), ELRSlyNTVATLYCV (p17Gag 74–88), SALSEGATPQDLNtMLNTVG (p24 41–60), FRDYVDRFFKTLRAEQA (p24 161–177), and SILDIKQGKEPFRDY (p24 149–164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85 LAI)  
**Epitope** SLYNTVATL  
**Subtype** B

**Immunogen**  
**Species (MHC)** human (A\*0205)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes that this epitope can be presented by A\*0201 and A\*0202.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (subtype A)  
**Epitope** SLYNTVATL  
**Subtype** A  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (A\*0201, A\*0214)  
**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.
- The epitope variants SLYNTVATL and SLfNTVATL were both recognized.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A02)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding  
**Keywords** subtype comparisons, escape, acute/early infection, variant cross-recognition or cross-neutralization, viral fitness and reversion, HLA associated polymorphism  
**References** Iversen *et al.* 2006

- The evolution of SLYNTVATL epitope was analyzed over 10 to 20 years in 76 patients and it was found that two opposing selective forces act on the epitope in HLA-A2+ patients. One is caused by an effective CTL pressure, resulting in escape. The main escape mutations were in positions 3, 6 and 8 of the epitope. The other force is selection for optimal viral growth, where the wild-type epitope's index amino acids are selected for. These common evolutionary pathways for the epitope were conserved across several HIV subtypes; while the balance between the opposing evolutionary pathways is suggested to determine variants in a patient at any given time. Fitness cost to SL9 variant generation leading to CTL escape also contributes to lower viral loads in such patients.
- Most variation in this epitope affects TCR recognition as shown by binding studies. Heterogenous CTL responses in patients to viral epitope variants also suggest that the advantage of any single mutation in SL9 is host (and HLA) dependent.
- CTL selection can differ between compartments as seen in compartmentalization of epitope variants between blood and cervix samples.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag (77–85 HXB2)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A02)  
**Assay type** Chromium-release assay, Other  
**Keywords** binding affinity, assay standardization/improvement  
**References** Bennett *et al.* 2007

- Standard assays like ELISpot, ICS and tetramer staining do not measure antiviral activity of HIV-infected CTLs, but use exogenous synthetic peptides on uninfected cells or HLA tetramers. Similarly, functional avidity assesses CTL activity against uninfected target cells. Here functional avidity is compared to the efficiency of actual infected cells' recognition and killing, revealing a sharp threshold between CTL immune antiviral activity and lack of infected cell recognition.
- As previously shown, epitopes and their variants spanned orders of magnitude of SD50. Likewise, CTL clearance of infected cells varied from 0 to 100% with epitope sequence variation. Moreover, direct suppression of HIV-1 replication by CTLs also varied with epitope variant.
- When killing efficiency (KE) using virus-infected cells was compared to functional avidity using synthetic peptides, there was a narrow threshold separating maximal killing from almost none. Since different SL9-specific clones had similar KEs, which were vastly different from RL10-specific CTL KEs, it was obvious that KEs varied with epitope sequence too. Finally, a strong correlation between KE and inhibition of viral replication was also seen.
- This epitope, SLYNTVATL, showed marked differences in its functional avidity, killing efficiency, as well as inhibition of viral replication when compared to its variants SLFNTVATL, SLfNTiATL, SLYNTiAvL, SLYNTiATL, SLYNaVATL and SLYNIVAvL.

**HXB2 Location** p17 (77–85)  
**Author Location**  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease  
**Species (MHC)** human (A02)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells  
**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p17 (77–85)  
**Author Location**  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A02)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, immunodominance, optimal epitope  
**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope SLYNTVATL elicited a magnitude of response of 335 SFC with a functional avidity of 0.05nM and binding affinity of 9.1nM.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag  
**Epitope** SLYNTVATL  
**Epitope name** SL-9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A02)  
**Assay type** Other  
**Keywords** escape, TCR usage, immune evasion  
**References** Yu *et al.* 2007b

- The dependence of TCR clonotype recruitment on genetic background was determined by studying monozygotic twins infected with the same HIV-1 strain. After an early, initial correlation in the magnitude, specificity and immunodominance of CTL response [Draenert *et al.* J. Exp. Med. 203:529-539(2006)], subsequent disease was mixed with respect to CTL epitopes' mutational escape. TCR alpha and beta chain repertoires were analyzed and it was found that their clonotypes in HIV-specific CTLs were broadly heterogeneous for both concordant and discordant epitope sequence evolution between the twins. Therefore initial TCR recruitment appears to be an entirely random process independent of genetic background of the infected individual.
- This epitope, SL9, showed discordant epitope evolution between the twins, and both alpha and beta TCR chains recruited were entirely different between them.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag (77–85)  
**Epitope** SLYNTVATL  
**Immunogen** vaccine  
*Vector/Type:* vaccinia  
**Species (MHC)** human (A2)  
**References** Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.

- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D<sup>d</sup> – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWYKYL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFD-SRL).
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- SLYNTVATL was recognized by 5/16 HLA-A2 patients.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease

**Species (MHC)** human (A2)

**Keywords** immunodominance

**References** Carruth *et al.* 1999

- The vaccine used was a live recombinant canarypox (CP) virus vaccine containing multiple HIV-1 genes (HIV-1 MN gp120, HIV-1 LAI gp41, HIV-1 LAI Gag, HIV-1 LAI protease).
- CD4+ and CD8+ Gag and Env specific CTL responses were detected in only 1/5 vaccinated volunteers, and were not detectable 1 year after vaccination.
- CTL responses to epitopes SLYNTVATL and TVYYGVPVWK from HIV+ control patients were used as positive controls.
- The study explored why vaccinees were non-responsive – non-response was not due to inherent defects or differences in the ability of these individuals to process and present antigen.
- Lack of response to SLYNTVATL led the authors to speculate that the immunodominance of this epitope in natural infections may not be recapitulated by vaccine antigen.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Callan *et al.* 1998

- Included as a negative control in a tetramer study of A2-EBV CTL response.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Wagner *et al.* 1998a

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1  $\alpha$  and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 HXB2)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Collins *et al.* 1998

- Two CTL clones recognize this epitope, but not the NL4-3 form of the epitope SLYNTIAVL.
- Nef down-regulates MHC class I molecules, which inhibits CTL killing, and this down-regulation can be partially compensated for by adding excess soluble peptide.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Durali *et al.* 1998

- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia.
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested.
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag.
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef.
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env.
- Patient B18 had the greatest breadth and diversity of response, and recognized Gag SLYNTVATL and Nef PLTFGWCFKL.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** dendritic cells

**References** Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.
- SLYNTVATL is a conserved HLA-A2 epitope included in this study – 3/6 patients had this sequence as their HIV direct sequence, one had the form SLYNTVAVL and all four of these had a detectable CTL response – the other two had either the sequence SLFSAVAVL or SLFSAVAAL and no detectable CTL response.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 IIIB)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- SLYNTVAVL, a variant found in HIV-1 MANC, was also recognized.
- SLFNTVAVL, a variant found in HIV-1 NY5CG, was also recognized.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is SLfNtvaTL.
- The D subtype consensus is SLyNTvATL.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** binding affinity

**References** Sewell *et al.* 1997

- Naturally occurring variants of this epitope escaped killing and acted as antagonists.
- The following variants were found in HIV-1 infected patients who mounted a strong response against this epitope: –F—, –F—V–, –S—, –SF—, –L—, —I—, —I–V–, –F–I—, –F–I–V–, –F–A—
- All variants bound to A2 with at least half the affinity of SLYNTVATL except the triple mutant: –F–I–V–
- Antagonism could be observed at low concentrations, abrogating lysis at an antagonist:agonist ratio of 1:10 – the antagonism was observed in one SLYNTVATL-specific CTL line but not another.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 HXB2)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** kinetics

**References** Yang *et al.* 1997b

- A chimeric universal T cell receptor was created by linking CD4 or an HIV-specific anti-gp41 Ig sequence to the signaling domain of the T cell receptor chain  $\zeta$ , and transduced into CD8+ cells.
- The response using universal-receptor-bearing CD8+ cells to lyse infected cells *in vitro* was comparable to the natural occurring responses of CTL-clones from HIV+ individuals in terms of kinetics and efficiency.
- A CTL clone specific for this epitope was used for the comparison.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A2)

**References** Stuhler & Schlossman 1997

- Keyhole limpet hemocyanin or tetanus toxoid Th epitope co-expression with peptide CTL epitopes on the same APC was required for induction of peptide-specific CTL.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Yang *et al.* 1996

- CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL.
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones.
- The distinction was thought to be due to lower expression of RT relative to Env and Gag.

- CTL can lyse infected cells early after infection, possibly prior to viral production.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CTL suppression of replication

**References** Yang *et al.* 1997a

- CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*.
- CTL produced HIV-1-suppressive soluble factors – MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, after antigen-specific activation.
- CTL suppress HIV replication more efficiently in HLA-matched cells.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 LAI)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Parker *et al.* 1992; Parker *et al.* 1994

- Examined in the context of motifs important for HLA-A2 binding.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 LAI)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** review

**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Tsomides *et al.* 1994

- CTL clones recognize naturally processed peptide.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (A2)

**References** Stuhler & Schlossman 1997

- A three cell-type cluster consisting of APCs, Th, and CTLs is the minimal regulatory unit required for Th cell-dependent induction of CTLs.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Cao *et al.* 1997a

- The consensus peptides of B and D clade viruses and some Cs have the sequence SLYNTVATL.
- The consensus peptide of A, and some C strains have SLFNTVATL, a form that is cross-reactive.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Dyer *et al.* 1999

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** escape

**References** Harrer *et al.* 1998

- Two overlapping epitopes were recognized in a long-term survivor, restricted by two different HLA molecules, HLA-A11(TLYCVHQR) and -A2 (SLYNTVATL)
- Viral sequence substitutions were present in this individual which did not affect viral replication and did not alter CTL-recognition of the A2 epitope, but reduced recognition of the A11 epitope, indicative of immune escape.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 SF2)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** acute/early infection

**References** Altfeld *et al.* 2001a

- The relative contribution of CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.

- The A2 epitopes Vpr AIIRLLQQL and p17 SLYNTVATL do not account for the dominance of Vpr and p17, the result holds even when HLA-A2+ individuals are excluded.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (BRU)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A2)

**Keywords** epitope processing, dendritic cells

**References** Buseyne *et al.* 2001

- Exogenous presentation or cross-presentation of epitopes by antigen presenting cells (APC) without protein synthesis is an alternative pathway for CTL epitope processing that may be important in the initial generation of viral specific CTL.
- Dendritic cells treated with AZT to inhibit protein synthesis were able to elicit a strong specific CTL response in SLYNTVATL specific CTL line EM71-1 without protein synthesis, while macrophages demonstrated a decreased presentation efficiency.
- Exogenous Gag epitope presentation was Env-dependent and required receptor-dependent fusion.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.
- In one patient with a SLYNTVATL response, no SLYNTVATL mutations were found among 21 clones despite high viral load (260,000 RNA copies/ml serum), suggesting low *in vivo* efficacy of the SLYNTVATL response.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART, immunodominance

**References** Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.
- 6/10 A\*0201+ individuals had HIV-specific tetramer staining cells, and 5 of these declined upon successful therapy.
- 4/10 A\*0201+ individuals with chronic HIV-1 infection recognized this epitope.
- Prior to therapy, the mean percentage of CD8+ cells that recognized the immunodominant epitope SLYNTVATL was six-fold greater than the percentage recognizing the epitope ILKEPVHGV.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART, TCR usage

**References** Islam *et al.* 2001

- Transcript frequencies were followed for four CTL clones from patient 115, with a chronic and stable HIV-1 infection, and tracked in a longitudinal study of samples collected 6-11 years post infection: clone M21 and E15 recognize ERYLKDQQL, and clone D87 recognizes variant ERYLQDQQL, and clone p175b recognizes the A2 epitope SLYNTVATL.
- This epitope sequence from clone p175b uses the Vβ5, CDR3 (FDS), Jβ2.7 TCR beta gene.
- Responses were stable even through HAART with undetectable viral loads, but frequencies varied over time by 100-fold, ranging from 0.012% of the total population for SLYNTVATL at its lowest point to 3.78% for M21, with the relative frequencies of clones shifting over time.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 SF2)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.

- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 2/6 group 2, and 2/4 group 3.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLFNTVATL

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A2)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- Variants SL(F/Y)NTVATL are A/B clade specific.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A2 women, 1/10 HEPS and 22/26 HIV-1 infected women recognized this epitope, likelihood ratio 18.3, *p* value < 0.003, and ILK(D/E)PVHGV tended to be more reactive in HEPS women, SL(F/Y)NTVATL in infected women.
- The dominant response to this HLA allele was to this epitope in the 1/10 HEPS case and in 18 of the 22/26 HIV-1 infected women that responded.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A\*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Subject ML 1250 had an A2 response to ILK(D/E)PVHGV prior to seroconversion, which switched to SL(F/Y)NTVATL post-seroconversion.
- Subjects ML 1575 and ML 1592 had no response to SL(F/Y)NTVATL prior to seroconversion, but made responses post-seroconversion.
- Subject ML 1760 had an A2 response to ILK(D/E)PVHGV prior to seroconversion, and gained responses to epitopes A2 SL(F/Y)NTVATL and B27 KRWII(L/M)GLNK post-seroconversion.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 93TH253 subtype CRF01)

**Epitope** SLYNTIATL

**Epitope name** G77-85

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV positive controls, and 0/9 HIV negative women that were not exposed.
- This epitope was reactive in HIV+ control study subjects 125 and 144 who carried HLA-A2.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 93TH253 subtype CRF01)

**Epitope** SLYNTIATL

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 2/4 tested FSWs recognized the E clade version of this epitope, SLYNTIATL, the B clade version is SLYNTVATL.
- This epitope was only conserved in CRF01 and subtypes B and D, and exact matches were uncommon.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- SLYNTVATL was the dominant A2 epitope recognized in patients with chronic infection, except for Subject 11841 who recognized 5/8 epitopes.
- Three subjects had an A2 response only to SLYNTVATL.
- The two subjects with acute infection did not respond to SLYNTVATL.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** mother-to-infant transmission, escape

**References** Goulder *et al.* 2001c



- Immune escape variants in this epitope were transmitted both horizontally and vertically in two families.
- Eight transmitting mothers and 14 non-transmitting mothers were studied and variation within the SL9 epitope was associated carrying HLA-A2 (P=0.04), but no link between variation from the SL9 consensus and vertical transmission was established.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (SF2)  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

**HXB2 Location** p17 (77–85)  
**Author Location**  
**Epitope** SLYNTVATL  
**Epitope name** Gag-SL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 17/30 (57%) recognized this epitope.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85 LAI)  
**Epitope** SLYNTVATL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** HAART, ART, epitope processing, immunodominance  
**References** Kelleher *et al.* 2001a

- Ritonavir (RTV) inhibits chymotryptic activity in the 20S proteasome *in vitro*, as does Saquinavir (SQV) to a lesser extent; Indinavir (IDV) does not. Thus there is concern protease inhibitors may adversely effect CTL epitope processing, but this paper indicates that processing is not inhibited at therapeutically relevant concentrations of RTV when the proteasome is functioning in an intracellular context.
- RTV did not reduce antigen presentation and concentration of the two immunodominant Gag CTL epitopes (KRWI-IMGLNK (B27) and SLYNTVATL (A2)).
- RTV did not inhibit the processing and assembly of HLA-B35 or -A2, which are assembled with a rapid and moderate time course, respectively, or of HLA-A3, -B27 and -B39.

**HXB2 Location** p17 (77–85)  
**Author Location** p17  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2002

- Neisseria gonorrhoea cervicitis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85 NL43)  
**Epitope** SLYNTVATL  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** class I down-regulation by Nef  
**References** Yang *et al.* 2002

- Nef down-modulates class I protein expression, and this study demonstrates directly that Nef-deleted HIV-1 NL-43 can be more effectively killed *in vitro* than NL-43 with an intact Nef. The effect was shown to be specific for class I presentation of epitopes, and unlike Nef, deleting Vpr did not alter CTL susceptibility of NL-43. The CTL clone 18030D23, specific for the class I A2 presented SLYNTVATL epitope, was one of four used in this study.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85 BRU)  
**Epitope** SLYNTVATL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** epitope processing  
**References** Cohen *et al.* 2002

- The antigen presentation of two A2-restricted epitopes was compared, SLYNTVATL (p17) and ILKEPVHGV (RT). HIV-1 infected cells were more sensitive to lysis by SLYNTVATL-specific CTL than by ILKEPVHGV-specific CTL, because of a higher density of SLYNTVATL-A2 resulting from differences in processing.
- Incubation with a T1-cell proteolytic extract showed that by four hours, 25% of a p17 peptide had a C-term Leu-85 and were SLYNTVATL-precursors, while ILKEPVHGV-precursors were far less frequent (6.8%) even with four times more proteolytic extract after 30 hours.
- p17 was preferentially cleaved between Leu85 and Tyr86, while appropriate Val484 and Tyr485 cleavage was minor for RT.
- In a competition experiment, RSLYNTVATL bound TAP 3.7-fold more efficiently than RT peptides.
- No difference in CTL avidity was detected in six patients with HLA-A2-restricted responses to these epitopes.
- No significant difference in HLA-A2 binding to p17 or RT epitopes was observed.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)**Epitope** SLYNTVATL**Immunogen** vaccine*Strain:* B clade IIIB *HIV component:* Gag, Pol *Adjuvant:* IL-12**Species (MHC)** mouse (A2)**References** Kmiecik *et al.* 2001

- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with either a p17-p24-p51 fusion protein (vG/P-92) or the Gag-Pol precursor protein (vVK1).
- Compared to vVK1, vG/P-92 induced a significant increase in Gag and Pol induced IFN $\gamma$  production and CTL responses, and to the epitopes SLYNTVATL and ILKEPVHGV, as determined by Elispot and 51Cr-release assays.

**HXB2 Location** p17 (77–85)**Author Location** Gag (77–85)**Epitope** SLYNTVATL**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Donor MHC** A2, A3, B7, Bw6**Keywords** HAART, ART**References** Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful antiviral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2–4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

**HXB2 Location** p17 (77–85)**Author Location** p17 (77–85 NL-43)**Epitope** SLYNTVATL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Keywords** class I down-regulation by Nef, escape**References** Ali *et al.* 2003

- NL43 was passaged in the presence of Nef KEKGGLEGL-specific CTL clones STD11 and KM3, giving rise to rapid selection of escape mutations, including E93G, E93K, K94N+G99R, G95R+G99R, E98K, E98D, G99R, G99E, L100P, and L100I; insertions, deletions, frameshifts and an early stop codon. 34/36 (94%) of sequences carried mutations in the epitope by seven days, 36/36 (100%) by 14 days.
- Several mutations selected by KEKGGLEGL-specific CTL were shown to impair the down regulation of class I MHC by Nef, in particular E93G, E93K, and a truncation mutation at position 51.
- Nef deletion mutants increased 100-fold NL-43 susceptibility to inhibition by CTL specific for epitopes in other proteins, the A2 epitopes ILKEPVHGV in RT and SLYNTVATL in p17 Gag.

**HXB2 Location** p17 (77–85)**Author Location** Gag**Epitope** SLYNTVATL**Epitope name** SL9**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** class I down-regulation by Nef**References** Bobbitt *et al.* 2003

- Nef, through Nef-mediated MHC-1 down-regulation, is not the only viral protein to influence levels of HIV-specific CTL recognition. The Rev L60F mutation, a common natural variant, can decrease CTL recognition of late gene products. The Rev mutation impacts the early to late gene switch, reducing late gene product production (Gag, Pol, Env, Vpu, Vpr and Vif), while increasing Nef production, both of which reduce the impact CTL recognition of late gene products. As expected, Rev L60F rendered HIV infected cells more resistant to CTL that recognized epitopes from the late proteins Env and Gag. Gag expression is reduced more than Env, and Gag-specific CTL were more profoundly affected. Conversely CTL against an epitope in an early gene product, Tat, were more efficiently recognized when infected with viruses carrying the Rev L60F mutation.
- Patients in the asymptomatic phase with active immune responses had more CTL resistant viruses, with lower Rev activity, lower Gag expression and greater resistance to Gag-specific CTL killing, while viruses isolated from people with AIDS were more sensitive to CTL killing.

**HXB2 Location** p17 (77–85)**Author Location** Gag (77–)**Epitope** SLYNTVATL**Epitope name** Gag77**Immunogen** HIV-1 infection, vaccine*Vector/Type:* peptide *HIV component:* Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)**Species (MHC)** human, transgenic mouse (A2)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** binding affinity, subtype comparisons, computational epitope prediction**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- 10/17 HIV-infected HLA-A2+ people in this study recognized this epitope, and CTL and CD8+ T cells responses were elicited by immunization of transgenic mice with this peptide.

**HXB2 Location** p17 (77–85)**Author Location** p17**Epitope** SLYNTVATL**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** Intracellular cytokine staining

**Keywords** immunodominance, genital and mucosal immunity

**References** Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T-cell responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T-cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 1/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A2, A24, B38, B60, Cw12, Cw2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), early treatment

**References** Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTAVTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Flow cytometric T-cell cytokine assay

**Keywords** responses in children

**References** Sandberg *et al.* 2003

- 65 vertically HIV-1 infected children, ages 1–16, the majority undergoing ART, were analyzed in regard to their plasma viremia and CD4+ and CD8+ T-cell counts, and CD8+ T-cell responses.
- Using vaccinia expressed Gag, Pol, Env, Rev, Nef in target cells in an Elispot assay, 85% of the children recognized at least one HIV antigen. Strong CD8+ T-cell responses were directed against Pol, followed by Gag and Nef. Children younger than 4 had significantly weaker responses (7/14 had no response) than older children (only 1/32 had no response, and responses were greater in magnitude).

- SLYNTVATL and ILKEPVHGV tetramers were used to quantitate specific responses. 49 children in an expanded cohort carried HLA-A2. 1/11 children under 3 years of age had detectable CD8+ T-cell responses to SLYNTVATL, 2/11 to ILKEPVHGV. Among children over 3, 11/38 recognized SLYNTVATL and 9/38 recognized ILKEPVHGV.
- Older children that maintained a CD4 count greater than 400 cells/ $\mu$ l tended to have stronger CTL responses.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** (A2)

**Donor MHC** A2, A3, B27, B51; A2, A3, B27, B57; A2, A23, B57

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining

**Keywords** assay standardization/improvement, memory cells

**References** Sun *et al.* 2003

- This study compares assay methods for testing CTL responses using samples from 20 HIV+ patients. The study compares ELISpot, tetramer-binding, and intracellular IFN- $\gamma$ . Tetramer-binding analysis was performed with Gag (SLYNTVATL) or Pol (ILKEPVHGV) tetramers. Antigen presentation using recombinant vaccinia viruses (rVVs) encoding HIV-LAI Gag, Pol, Env, Nef, Tat and Vif proteins was compared to peptide panels. HIV antigen recognition in memory CTLs was measured by chromium release assay and compared to effector/memory CD8+ T-cells in an IFN- $\gamma$  ELISpot assay.
- Results: IFN- $\gamma$  Elispot and flow cytometry gave similar frequencies of HIV specific CD8+ T-cells. Tetramer-binding analysis was most sensitive. Pools of peptides and the sum of frequencies of individual peptides were comparable. Elispot assays using peptides were more sensitive than assays using vaccinia expressed proteins. Cr release and Elispot against rVVs gave comparable memory cell responses 2/3s of the time.
- 3/7 HLA-A2+ patients recognized this epitope.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 NL43)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** Chromium-release assay, CTL suppression of replication

**Keywords** escape, TCR usage

**References** Yang *et al.* 2003a

- Virus was cultured in the presence of CTL lines specific for 5 different epitopes (SLYNTVATL, ILKEPVHGV, IEIKDTKEAL, SEGATPQDL, and KEKGGLEGL) to study the emergence of escape mutations. Escape varied between clones for the same epitope, and between different epitopes. Gag and RT epitope escape, if it occurred at all, tended to

be monoclonal and within the epitope, indicating strong fitness constraints, while the Nef epitope escape was rapid, polyclonal, and sometimes the result of upstream frameshifts.

- Three CTL clones were studied that recognized SLYNTVATL, 161JxA14, 18030D23, and 115DEC4. The different TCR usage on the CTL clones resulted in different patterns of recognition and escape. 161JxA14 suppressed the variant sIFntvatl, 18030D23 did not; conversely the variants sIFntIaV1 and sIFntIatI were suppressed by 18030D23, but not 161JxA14.
- After two weeks of passage the predominant escape mutant from 161JxA14 was slyntIatI. Amino acid residues flanking SL9 were unchanged. Escape mutations did not occur within two weeks for the two additional SL9-specific CTL clones 18030D23 and 115DEC4.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (43)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A2)

**Assay type** CTL suppression of replication

**Keywords** class I down-regulation by Nef, early-expressed proteins, kinetics

**References** Ali *et al.* 2004

- Translocation of the gag SLYNTVATL epitope into the early expressed Nef protein resulted in increased antiviral efficiency of SL9 specific CTLs in culture and the loss of MHC-I down-regulation by Nef, indicating that both the timing of epitope expression and reduction of MHC-I affect the ability of CTLs to suppress HIV-1.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85 B con)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** variant cross-recognition or cross-neutralization

**References** Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2–39) epitopic regions were targeted in an average of 6 proteins (range, 1–8). HAART resulted in decrease in antigen and reduction in gamma IFN EliSpot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.

- 3 subjects recognized this epitope with high functional avidity. Relative to consensus, 2 individuals that had the SLYNTVATL epitope carried a R -> K mutation proximal to but outside the epitope; possible processing implications were not studied here.

**HXB2 Location** p17 (77–85)

**Author Location** Gag

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Koning *et al.* 2004

- A high-risk seronegative group of 29 patients showed reduced in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- 2/11 HLA A2+ infection-resistant men, compared to 7/9 men pre-seroconversion who went on to become infected, reacted to this epitope.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 14/19 patients recognized this epitope, it was the most commonly recognized of 9 HLA A\*02 epitopes tested.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** Chromium-release assay

**Keywords** binding affinity, TCR usage, characterizing CD8+ T cells

**References** Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 3/14 CTL T-cell clones tested were specific for Gag/p17-SL9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 range for Gag/p17-SL9 was 1,000 - 20,000 pg/ml.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, memory cells, characterizing CD8+ T cells

**References** Daniel *et al.* 2004

- CD4+ and CD8+ responses in chronically HIV-1 infected patients on HAART were weak with decreased polyclonality. Only 33% of patients had CD4+ T-cells that could proliferate, and only 22% had HIV-specific CD8+ T-cell responses, and those rare responses showed low perforin levels and persistent expression of CD27, indicating incomplete differentiation and loss of lytic function.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** proliferation, Tetramer binding, T-cell Elispot

**Keywords** acute/early infection, characterizing CD8+ T cells, immune dysfunction

**References** Lichterfeld *et al.* 2004a

- HIV-1 specific CD8+ T-cells in acute and long-term nonprogressive HIV-1 infection show strong ex-vivo proliferative capacities which are rapidly lost in chronic HIV-1 infection. The loss of CD8+ T-cell function is closely linked with the loss of HIV-1 specific, IL2 secreting CD4+ T-cells. The function can be rescued in vitro and in vivo by restoring the specific CD4+ T-cell help.
- Despite being detectable at high frequencies, CD8+ T-cells specific for SL9 epitope were shown to entirely lose their proliferative capacity in chronic HIV-1 infection. This activity

could be restored by co-stimulation with CD4+ T cells isolated from acute infection in an IL-2 dependent manner.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Epitope name** gag 77-85

**Subtype** B

**Immunogen** HIV-1 infection, HIV-2 infection

**Species (MHC)** human (A2)

**Country** Gambia

**Assay type** Tetramer binding, Intracellular cytokine staining

**Keywords** escape, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, HIV-2

**References** Lopes *et al.* 2003

- CD8+ T cells from HIV-2 infected patients had more polyclonal TCR responses than HIV-1 infected patients, who tended to have oligoclonal responses. This results in limited plasticity of T cell responses to amino acid substitutions within epitopes in HIV-1 infections. HIV-2-specific CD8+ T-cells showed a more diverse TCR usage associated with enhanced CD8 expansion and IFN-gamma production on cross-recognition of variant epitopes.
- Responses to this epitope were characterized in detail. One patient's response to SL9 A2-SLYNTVATL tetramers was shown to have only Vbeta5.1 clonotypes. The naturally-occurring HIV-2 variant: sIFntvCVI, was not recognized well by this response or by the SLYNTVATL reactive CD8+ T cells in four additional A2+ HIV infected asymptomatic individuals. The subtype A variant, sIFntvatl was also poorly recognized, and 4/5 Ala substitutions abrogated responses. All variants bound to HLA-A2 with higher affinity than the index peptide except slyntAatl, which was slightly reduced, so the lack of cross-reactivity must have been due to the TCR.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** Chromium-release assay

**Keywords** assay standardization/improvement

**References** Lubong *et al.* 2004

- Using IL7 or IL15 in culturing of HIV-1-specific CTL clones was inferior to using IL-2 alone; the addition of these cytokines to IL-2 did not show any advantage. Neither proliferation, survival, nor lytic capacity of HIV-1-specific CTLs was significantly enhanced by addition of IL7 or IL15.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A2)

**Donor MHC** A\*02, A\*30, B\*15, B\*4402

**Assay type** Tetramer binding, T-cell Elispot

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 4/8 HIV epitopes tested in an IFN $\gamma$  EliSpot assay or tetramer assay. Responses were detected 8 and 28 weeks after exposure. No response to SLYNTVATL was detected by either assay.

**HXB2 Location** p17 (77–85)**Author Location** p17**Epitope** SLYNTVATL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** United Kingdom**Assay type** Tetramer binding, T-cell Elispot, Intracellular cytokine staining**Keywords** rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction**References** Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

**HXB2 Location** p17 (77–85)**Author Location** p17 (77–85)**Epitope** SLFNTVATL**Epitope name** SLF**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, escape**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0–80% as efficiently as the index peptide, and the relatively efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.

- This epitope was one of six epitopes found to be under positive selection for escape mutations and was completely replaced by escape variants between days 327 and 635 (sLYntvatl and sLYnAvatl).

**HXB2 Location** p17 (77–85)**Author Location** Gag**Epitope** SLYNTVATL**Epitope name** SL9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Two escape mutations, at positions 3 and 8, sIFntvatl and slyntvaVI, were found in the most polymorphic residues in the epitope. These were shared between clades B and C. One escape mutation, at position 6, slyntlatl, was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** p17 (77–85)**Author Location** p17 (77–85)**Epitope** SLYNTVATL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding**Keywords** acute/early infection, optimal epitope**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This is the most commonly recognized A2 epitope in chronic infection, recognized in 62% of 74 A2+ people, but it is rarely recognized in acute infection (in only 1/14 cases).

**HXB2 Location** p17 (77–85)**Author Location** p17 (77–85 HXB2)**Epitope** SLYNTVATL**Epitope name** 17A**Subtype** B**Immunogen** vaccine*Vector/Type:* DNA *Strain:* multiple epitope immunogen *HIV component:* p17/p24 Gag, Pol *Adjuvant:* IL-12**Species (MHC)** transgenic mouse (A2)**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** vaccine-specific epitope characteristics, vaccine antigen design

**References** Bolesta *et al.* 2005

- Immunization of transgenic mice with a codon-optimized hGagp17p24-Polp51 DNA plasmid, consisting of clusters of highly conserved CTL epitopes presented by multiple MHC class I alleles, induced 2- to 5-fold higher CD8+ T-cell responses than the corresponding full-length proteins. The modified proteins had the ribosomal frameshift deleted, as well as the potentially immunosuppressive p15, and protease and integrase. This correlated with higher protection against challenge with Gag and Pol expressing recombinant vaccinia virus. Mice immunized with the hGagp17p24-Polp51 also showed an elevated level of type 1 cytokine production as well as an increased titer of p24- and RT-specific IgG2 antibody responses.
- This was 1 of 4 A2 gag/pol epitopes tested. Transgenic mice immunized with the deleted construct induced more potent EliSpot reactions to this epitope than those immunized with full length Gag/Pol.

**HXB2 Location** p17 (77–85)**Author Location** p17 (77–85)**Epitope** SLYNTVATL**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Donor MHC** A2A2, B44, B70; A2, A31, B51, B58w4**Country** United States**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay**Keywords** HAART, ART, escape, variant cross-recognition or cross-neutralization**References** Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- This epitope was recognized in 2 individuals and was invariant in both prior to HAART (20/20 clones in each).

**HXB2 Location** p17 (77–85)**Author Location****Epitope** SLYNTVATL**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** Germany**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, escape, variant cross-recognition or cross-neutralization, optimal epitope**References** Harrer *et al.* 2005

- An HLA-B13-restricted optimal epitope was defined in Nef, RI9. The frequency of CTLs specific for this epitope in B13-positive patients exceeded the number of CTLs against other epitopes, indicating that this is a dominant epitope in B13-positive subjects. Three B13-positive patients who had an immunodominant response to this epitope were good controllers of their infection, with low viral loads over long periods.
- Five A2+ B13+ patients were found to make an immunodominant response to the B13 epitope RI9. 0/5 recognized ILKEPVHGV, and only 1/5 recognized SLYNTAVTL, with a much lower frequency than the B13 response.

**HXB2 Location** p17 (77–85)**Author Location** Gag (77–85 BRU)**Epitope** SLYNTVATL**Subtype** B, CRF02\_AG**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** Cote D'Ivoire**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivorian subjects.
- This epitope was recognized by 3/9 CRF02\_AG-infected patients, and by 2/9 B-infected patients.

**HXB2 Location** p17 (77–85)**Author Location** Gag**Epitope** SLYNTVATL**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** Netherlands**Assay type** Tetramer binding, Flow cytometric T-cell cytokine assay**Keywords** binding affinity, rate of progression, escape, characterizing CD8+ T cells**References** Jansen *et al.* 2005

- HLA-B57 has been associated with long term non-progression in HIV+ people. The number and responsiveness of CD8 T-cells directed to different Gag peptides presented by HLA-A2, -B8 and B57 were compared. T cells specific for the HLA-B57 epitope KAFSPEVIPMF responded to a higher extent and more readily to antigenic stimulation than those specific for the A2 epitope SLYNTVATL and the B8 epitope EIYKRWII.
- In 3/4 A2 subjects that were sequenced, epitope variants dominated: 2 subjects carried sIFntvatl, and the other slyntlatl.
- Tetramer decay experiments indicate that the HLA-B57 peptide has a higher half-life than the A2 and B8 peptides. The authors point out that CD8+ T cells with high binding affinity may require less help.

**HXB2 Location** p17 (77–85)**Author Location** Gag (77–85)**Epitope** SLYNTVATL**Epitope name** SL9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Donor MHC** A\*02, A\*68, B\*14, B\*52, Cw\*08, Cw\*12**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** escape, optimal epitope**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- Elispot responses to the consensus form of this epitope, SLYNTVATL, were much more intense than to the most common variants of the epitope found over time in this individual, SLfNTiATL and SLfNTVAvL; these may be escape variants. The strong response to the consensus form persisted, despite the fact it was not observed among the autologous sequences during 6 years of chronic infection.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Subtype** B  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (A2)  
**Country** Canada  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance, genital and mucosal immunity, characterizing CD8+ T cells  
**References** Makedonas *et al.* 2005

- CD8 T-cell responses were studied in individuals who remained seronegative in spite of being mucosally (group 1) or intravenously (group 2) exposed to HIV-1. A similar proportion of subjects from each group recognized at least 1 HIV peptide, and they recognized peptides with similar cumulative intensity. The proportion of responding individuals in both groups was significantly greater than in a low-risk, negative control group. One exposed uninfected subject recognized 7 epitopes.
- HLA-A\*0201 epitopes that are immunodominant in chronically infected individuals were rarely stimulatory in exposed uninfected individuals. SLYNTVATL was recognized by one HLA A2+ individual in each group (1/11 vs 1/5), while none of the exposed uninfected individuals tested responded to ILKEPVHGV. In contrast, chronically infected subjects recognized these epitopes at a frequency of 69% and 31%, respectively.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** Germany  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** HAART, ART, characterizing CD8+ T cells, optimal epitope  
**References** Schmitt-Haendle *et al.* 2005

- CTL responses to 3 HLA-A2-restricted epitopes were investigated in 51 HIV-1 infected HLA-A2+ individuals. The most prevalent response was seen for IV9, followed by SL9. The VL9 epitope was not recognized. There was a significant correlation of CTL activity to the CD8 counts in peripheral blood, but no correlation to CD4 counts, viral load, or antiviral therapy.
- SL9 was only recognized in 13.7% of the individuals tested.

**HXB2 Location** p17 (77–85)  
**Author Location** p17  
**Epitope** SLYNTVATL  
**Epitope name** A2-SL9(p17)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p17 (77–85)  
**Author Location** p17 (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Subtype** B  
**Immunogen** peptide-HLA interaction  
**Species (MHC)** human (A2)  
**Assay type** Chromium-release assay, HLA binding  
**Keywords** escape, TCR usage, structure, optimal epitope  
**References** Martinez-Hackert *et al.* 2006

- Several natural SL9 variants were shown to bind comparably well to soluble HLA-A2 and D3 TCR. All variants had remarkably similar peptide conformations as evidenced by high resolution crystal structures of soluble interacting proteins. These structures were shown to differ from other peptide-MHC-TCR structures. SL9 variation was shown to be partially restricted by its context in the HIV p17 matrix protein, and the preservation of peptide conformation despite epitope variation may contribute to the persistence of SL9-mediated immune responses.



- 11 Natural variants of SLYNTVATL were tested. They were SLYNTiATL (SL9-6I), SLYNTiAvL (SL9-6I/8V), SLYNTVAvL (SL9-8V), SLfNTVATL (SL9-3F), SLfNTiAvL (SL9-3F/6I/8V), SLfNTiATL (SL9-3F/6I), SLfNTVAvL (SL9-3F/8V), SLYNaVATL (SL9-5A), SLYNsVATL (SL9-5S), SLYNaiATL (SL9-5A/6I), SLYNIVAvL (SL9-5L/8V). Only variants at P5 where Threonine is substituted by Alanine or Leucine abrogated activity, while all others variants were active. No natural variants had substitutions at P4, while P1, P2 and P9 were also conserved. 9 synthetic variants were also tested.
- This degenerate recognition of the HIV Gag epitope by CTL is different from other viral peptide-degeneracies in that several CTL clones can perform equally well in recognition of the SL9 pMHC, and there is not necessarily one dominant recognition.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human, mouse (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** TCR usage, variant cross-recognition or cross-neutralization

**References** Kan-Mitchell *et al.* 2006

- A synthetic combinatorial nonapeptide library was screened with ex-vivo-primed SL9-specific T-cells and an agonist variant of the SL9, p41 SLYNTVAA<sub>L</sub>, was identified. p41 immunized SL9-cross-reactive CTLs from donors ex vivo and double knockout mice expressing a chimeric HLA I molecule. p41-primed CTLs were also found to require less costimulation from APCs and (unlike SL9-CTLs, they required exogenous IL-2 to proliferate, suggesting they would have better immune memory) less need for exogenous IL-2 to proliferate. The loss of SL9 T-cells was minimized with p41, and the TCR clonotype was shown to be able to develop into either help-dependent or help-independent CTLs.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATL

**Epitope name** Peptide 7027

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A2, A3, B44, B7

**Country** United Kingdom

**Assay type** Flow cytometric T-cell cytokine assay, Other

**Keywords** HAART, ART, immunodominance, TCR usage, memory cells

**References** Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish

even with the relative preservation of functional memory responses. Maintenance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

**HXB2 Location** p17 (77–85)

**Author Location** Gag

**Epitope** SLYNTVATL

**Epitope name** A2-SL9 Gag (77-85)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A2, A32, B27, B39

**Country** France

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, immunodominance, characterizing CD8+ T cells

**References** Almeida *et al.* 2007

- Since it is suggested that a single response to B27-KK10 epitope may be responsible for the association of HLA-B\*2705 patients with AIDS-free survival, B27-KK10-specific CTLs were compared to other HLA-specific CTLs in phenotype, function, clonal diversity, and antigen sensitivity in 47 treatment-naive infected slow or nonprogressing patients.
- cVL, the cell-associated viral load (number of infected cells harboring HIV DNA) correlated inversely with Gag-specific CTLs. This was most significant in HLA-B27 donors, and KK10 was identified as the peptide generating strongest CTL responses.
- B27-KK10-specific CTLs had no significant phenotypic differences from other epitope-specific CTLs upon testing a large panel of markers; however, they released higher proportions of IFN-gamma, TNF-alpha, MIP-1beta and CD107a upon antigenic stimulation.
- Both B27-KK10-specific and other HLA-specific CTLs had strikingly consistent domination of single clonotypes, as shown by analyses of TCRB gene expression. B27-KK10-specific CTLs showed no preferential usage of CDR3 motifs, indicating that they could be recognized by diverse clonotypes with differing binding properties. Over several years, B27-KK10-specific CTLs changed their dominant clonotype as compared to other CTLs. This temporal dominant clonal turnover was attributed to a decline in replicative capacity of the dominant clonotype as seen by increases in CD57 expression, which is linked to replicative senescence.
- Studies involving functional avidity and different HLA-restricted responses proved that B27-KK10 responses had highest avidity. An inverse correlation between patient cVL and functional avidity of both dominant and highest subdominant responses suggested that functional avidity correlates with capacity to control HIV replication via infected cell elimination.
- Using the example seen in one patient, the authors stress the importance of maintaining protective stimulating activity of CTLs. When control by dominant clonotypes is lost, as in viral escape, ensuing viral replication is rapid.
- SLYNTVATL, was a dominant epitope found in non-B27-KK10 CTL responses.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag  
**Epitope** SLFNTVATL  
**Epitope name** A2-SL9 Gag (77–85)  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A2, A3, B60, B7  
**Country** France  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** binding affinity, immunodominance, characterizing CD8+ T cells  
**References** Almeida *et al.* 2007

- Since it is suggested that a single response to B27-KK10 epitope may be responsible for the association of HLA-B\*2705 patients with AIDS-free survival, B27-KK10-specific CTLs were compared to other HLA-specific CTLs in phenotype, function, clonal diversity, and antigen sensitivity in 47 treatment-naïve infected slow or nonprogressing patients.
- cVL, the cell-associated viral load (number of infected cells harboring HIV DNA) correlated inversely with Gag-specific CTLs. This was most significant in HLA-B27 donors, and KK10 was identified as the peptide generating strongest CTL responses.
- B27-KK10-specific CTLs had no significant phenotypic differences from other epitope-specific CTLs upon testing a large panel of markers; however, they released higher proportions of IFN- $\gamma$ , TNF- $\alpha$ , MIP-1 $\beta$  and CD107a upon antigenic stimulation.
- Both B27-KK10-specific and other HLA-specific CTLs had strikingly consistent domination of single clonotypes, as shown by analyses of TCRB gene expression. B27-KK10-specific CTLs showed no preferential usage of CDR3 motifs, indicating that they could be recognized by diverse clonotypes with differing binding properties. Over several years, B27-KK10-specific CTLs changed their dominant clonotype as compared to other CTLs. This temporal dominant clonal turnover was attributed to a decline in replicative capacity of the dominant clonotype as seen by increases in CD57 expression, which is linked to replicative senescence.
- Studies involving functional avidity and different HLA-restricted responses proved that B27-KK10 responses had highest avidity. An inverse correlation between patient cVL and functional avidity of both dominant and highest subdominant responses suggested that functional avidity correlates with capacity to control HIV replication via infected cell elimination.
- Using the example seen in one patient, the authors stress the importance of maintaining protective stimulating activity of CTLs. When control by dominant clonotypes is lost, as in viral escape, ensuing viral replication is rapid.
- SLFNTVATL was a dominant epitope found in non-B27-KK10 CTL responses.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag (77–85 Henan isolate)  
**Epitope** SLYNTVAVL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)

**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- SLYNTVAVL was recognized by 61% HLA-A2-positive individuals.

**HXB2 Location** p17 (77–85)  
**Author Location** Gag (77–85)  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A\*0201, A\*2402, B\*4001, B\*5001, Cw03, Cw04  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization  
**References** Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, SLYNTVATL (SL9), is restricted by HLA-A02. A variant that arose was SLYNTVAvL.

**HXB2 Location** p17 (77–85)  
**Author Location**  
**Epitope** SLYNTVATL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** United States, South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding  
**Keywords** memory cells  
**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated

impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** p17 (77–85)

**Author Location**

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining

**Keywords** responses in children, rate of progression

**References** Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking attribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Response detected in 1 long-term surviving progressive child.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Epitope name** SL9

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A\*0202, A2)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope, SLFNTVATL, was preferentially recognized by CTL.
- This epitope was recognized by two different exposed seronegative prostitutes.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** review, escape

**References** Sewell *et al.* 2000

- Review of the impact of CTL on viral immunity and escape that notes that SLYNTVATL-tetramer binding cells in individuals that react to this epitope inversely correlate with plasma viral load.

**HXB2 Location** p17 (77–85)

**Author Location** (SF2, HXBc2/Bal chimeric)

**Epitope** SLYNTVATL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)**

**Keywords** rate of progression, escape

**References** Douek *et al.* 2002

- Seven HIV-positive subjects tended to make their strongest CD8+ T-cell response against Gag; these responses had varying breadth and magnitude that were unrelated to disease progression.
- Patient TX7 primarily recognized SL9 during a three year study period and used six T-cell clonotypes for this recognition.
- SLYNTVATL was the only form of the epitope found initially, but three alternate forms eventually appeared: SLYNTVAVL, SLYNTIATL, and most commonly SLYNTI AVL. These distinct forms bind A2, but have distinct abilities to stimulate different T-cell clonotypes.
- In subject TX7, the observed mutations of SL9 failed to escape overall CTL recognition, presumably because the six T-cell clonotypes allowed a more flexible response.
- The BV17 T-cell clone recognized SL9 but not SLYNTI AVL, and BV17 became undetectable at week 20 when SLYNTI AVL predominated. Subsequently BV17 became the second most common clone. Thus the relative frequency of the T-cell clonotypes varied with respect to each other and to epitope variation.

**HXB2 Location** p17 (77–85)

**Author Location** p17 (77–85 LAI)

**Epitope** SLYNTVATL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0201

**Keywords** HAART, ART, responses in children

**References** Luzuriaga *et al.* 2000

- Longitudinal study of 8 infants with prolonged viral suppression due to combination antiretroviral therapy showed no HIV-1 specific CTL responses in peripheral blood cells. 6/8 were studied using a Chromium release assay and no response was detected using Gag expressed in vaccinia in the target cells. Three HLA-A\*0201 children were tested using SLYNTVATL or ILKEPVHGV HLA A\*0201 tetramers and again no HIV-specific response was detected, either using PBMC specimens, or PBMC which had been stimulated *in vitro* for a week.
- In contrast, one of the children with therapy suppressed HIV viral replication who was co-infected with HIV and EBV, while HIV-tetramer negative, had EBV-tetramer staining cells at a frequency of 0.14% in the PBMC.

**HXB2 Location** p17 (77–85)

**Author Location** Gag (77–85)

**Epitope** SLYNTVATL

**Subtype** B

**Immunogen** peptide-HLA interaction

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Degranulation, CD107a and b cell surface mobilization, HLA binding

**Keywords** binding affinity, co-receptor

**References** Laugel *et al.* 2007b

- To interrogate why epitope variant-related T-cell activations differ in degree of CD8 coreceptor dependence, the authors set up a system to examine pMHC/CD8 interactions upon binding of antigenic ligands by CTLs. 2 previous hypotheses to explain coreceptor dependence are those of Holler and Kranz suggesting it is inversely correlated to TCR/pMHC affinity, or it is related to the geometry of TCR engagement. The former hypothesis was supported, since the CD8 coreceptor may optimize T-cell polyspecificity by improving low to intermediate binding affinities of pMHC for TCR.
- Most studies were performed using clones specific for an hTERT or HTLV-1 peptide. SLYNTVATL was used with clones 003 and SLY-10, both derived from HIV-infected donors, to show that binding to pMHC tetramers was greater in the presence of WT rather than null CD8 coreceptors.

**HXB2 Location** p17 (77–85)

**Author Location**

**Epitope** SLYNTVATL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A\*0201, A\*1101; B\*4002, B\*5101

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it both before and after infection.
- PBMCs from reacting individual failed to bind the HLA-A2/SLYNTVATL tetramer. The optimal epitope turned to be newly defined LYNTVATL, restricted by HLA-C14, not previously shown to restrict HIV-1 epitopes, and T cells recognizing LYNTVATL were of high avidity.

**HXB2 Location** p17 (77–85)

**Author Location** p17

**Epitope** SLYNTVATL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** assay standardization/improvement

**References** Willberg *et al.* 2007

- In order to detect CTL responses using fewer PBMCs and sets of peptides, the authors select pools of peptides that correspond to epitopes which are most likely to elicit HIV-1-specific immunogenic response in the population under study i.e. epitopes that interact with the major HLA of the population. This approach is of benefit to in-field therapeutic and vaccine studies and also under resource-limiting conditions.
- Peptide panels for the following proteins were also generated and tested - p17, p24, p2p7p2p6, Protease, RT, Integrase, Tat, Rev, Vif, Vpr, Vpu, Env and Nef.

**HXB2 Location** p17 (77–86)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATLY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, SLYNTVATLY, was detected within overlapping peptides TGSEELRSLYNTVATLY and SLYNTVATLY-CVHQRIEV as well as overlapping peptide QLQPSLQT-GSEELRSLY.

**HXB2 Location** p17 (77–86)

**Author Location** Gag

**Epitope** SLYNTVATLY

**Epitope name** 1261

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A01, A02, B08, Cw16; A02, A30, B35, B49, Cw04, Cw07; A02, A03, B58, B7, Cw07; A02, A03, B08, B51, Cw01, Cw07

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which

four were recognized as promiscuous epitopes and five as MHC supertypes.

- Estimated binding probability for SLYNTVATLY: 78%

**HXB2 Location** p17 (77–86)

**Author Location**

**Epitope** SLYNTVATLY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining

**Keywords** responses in children, rate of progression

**References** Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking attribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Response detected in 1 LTNP child and 1 early non-progressive child.

**HXB2 Location** p17 (77–86)

**Author Location** Gag (82–92)

**Epitope** SLFNTVATLY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p17 (77–91)

**Author Location** p17 (77–85)

**Epitope** SLYNTVATLYCVHQR

**Subtype** A, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*3002)

**Donor MHC** A\*3002, A\*6801, B\*5703, B\*5802; A\*0201, A\*2902, B\*1402, B\*1503

**Country** Uganda

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

**References** Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade,

while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.

- The sequence contains a known A2 epitope and a known A\*3002 epitope, and the subjects recognizing it each carry an HLA with a previously-defined restriction. The viral sequence isolated from the subjects was sIFntvatlycvhqr, and was reactive.

**HXB2 Location** p17 (77–94)

**Author Location** p17

**Epitope** SLYNTVATLYCVHQRIEV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, SLYNTVATLYCVHQRIEV, had an overall frequency of recognition of 25.3% - 30.5% AA, 26.9% C, 22.7% H, 9.5% WI. This peptide is included in a 34 aa Gag-p17 highly reactive region to be used for vaccine design.

**HXB2 Location** p17 (78–85)

**Author Location** p17

**Epitope** LYNTVATL

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on a patient with an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p17 (78–85)

**Author Location**

**Epitope** LYNTVATL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human (C14)

**Donor MHC** A\*0201, A\*1101; B\*4002, B\*5101

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it both before and after infection.
- This epitope was contained in SLYNTVATL epitope, but PBMCs from reacting individual failed to bind the HLA-A2/SLYNTVATL tetramer. The optimal epitope turned to be newly defined LYNTVATL, restricted by HLA-C14, not previously shown to restrict HIV-1 epitopes, and T cells recognizing LYNTVATL were of high avidity.

**HXB2 Location** p17 (78–85)

**Author Location**

**Epitope** LYNTVATL

**Immunogen**

**Species (MHC)** human (Cw\*14)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an Cw14 epitope.

**HXB2 Location** p17 (78–86)

**Author Location** (C consensus)

**Epitope** LYNTVATLY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*29)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the Y2 residue of LYNTVATLY are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** p17 (78–86)

**Author Location** p17 (78–86)

**Epitope** LYNTVATLY

**Immunogen**

**Species (MHC)** human (A\*2902)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an A\*2902 epitope.

**HXB2 Location** p17 (78–86)

**Author Location** (78–86)

**Epitope** LFNTVATLY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2902)

**Assay type** Other

**Keywords** HLA associated polymorphism

**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- All HIV-1 subtype C protein sequences were analysed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid

with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.

- LFNTVATLY was a previously defined A\*2902 presented epitope that encompassed an A\*29 associated polymorphism, LfNTVATLY, in the second position.

**HXB2 Location** p17 (78–86)

**Author Location** p17

**Epitope** LYNTVATLY

**Epitope name** LY-9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2902, B\*4403)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA

**References** Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. This is 1 of 5 novel epitopes that were found among subtype C HIV-1 from African patients who hadn't previously been identified in B clade infections. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles.
- LYNTVATLY was presented by A\*2902 and B\*4403. B\*44 is more common among Caucasians than Zulus (allele frequency 0.149 versus 0.107), while A\*29 is more common in Zulus (0.045 versus 0.125).

**HXB2 Location** p17 (78–86)

**Author Location** (C consensus)

**Epitope** LYNTVATLY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A29)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p17 (78–86)

**Author Location**

**Epitope** LYNTVATLY

**Immunogen**

**Species (MHC)** human (B\*4403)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B\*4403 epitope.

**HXB2 Location** p17 (80–88)

**Author Location** Gag (80–)

**Epitope** NTVATLYCV

**Epitope name** Gag80

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* p17

*Gag Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.

**HXB2 Location** p17 (82–91)

**Author Location** p17 (82–91 93TH253 subtype CRF01)

**Epitope** IATLWCVHQR

**Epitope name** G82-91

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 265 who was HLA A2/A11.
- This epitope was strongly reactive in HIV+ study subject 053 who carried HLA-A11.

**HXB2 Location** p17 (82–91)

**Author Location** p17 (82–91 93TH253 subtype CRF01)

**Epitope** IATLWCVHQR

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined.
- 3/8 tested FSWs recognized this epitope.
- This epitope was not conserved in other subtypes, and exact matches were uncommon.

**HXB2 Location** p17 (83–91)

**Author Location** p17 (84–91)

**Epitope** ATLYCVHQR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This putative epitope, ATLYCVHQR, was detected and confirmed within overlapping peptides TGSEELRSLYNTVATLY and SLYNTVATLYCVHQRIEV.

**HXB2 Location** p17 (83–91)

**Author Location** Gag (Henan isolate)

**Epitope** AVLYCVHQR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (84–91)

**Author Location** p17 (84–91)

**Epitope** TLYCVHQK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an A\*1101 epitope.

**HXB2 Location** p17 (84–91)

**Author Location** Gag (83–90)

**Epitope** TLYCVHQR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** subtype comparisons, TCR usage

**References** Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A\*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A\*1101 epitopes was recognized in a clade specific manner. Two other HLA A\*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- TLYCVHQR was found to elicit clade-specific responses in clade B (TLYCVHQR is most common, and is also common in clade A – the variant tlycvhqK is common in clade B) and clade E (tIWcvhqr is most common). TLYCVHQR was not recognized by any CTL, tlycvhqK was recognized by CTL from 1/5 B clade infected Japanese subjects, and tIWcvhqr was not recognized by CTL from infected Thai subjects, so this seems to be a B clade exclusive epitope.
- The binding of the variant peptides to HLA A\*1101 was comparable, but CTL that recognized tlycvhqK did not cross-recognize the other forms, implicating TCR interaction differences.

**HXB2 Location** p17 (84–91)

**Author Location** p17 (83–91)

**Epitope** TLYCVHQR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** escape

**References** Harrer *et al.* 1998

- Two overlapping epitopes were recognized in a long-term survivor, restricted by two different HLA molecules, HLA-A11(TLYCVHQR) and HLA-A2 (SLYNTVATL)



- Viral sequence substitutions were present in this individual which did not affect viral replication and did not alter CTL-recognition of the A2 epitope, but reduced recognition of the A11 epitope, indicative of immune escape.
- A Q90E substitution resulted in a loss of the ability of the peptide to induce lysis, a R91K substitution was still reactive, and a R91Q substitution showed a reduced ability to stimulate lysis.

**HXB2 Location** p17 (84–92)

**Author Location** Gag (83–91 SUMA)

**Epitope** TLYCVHQKI

**Epitope name** Gag TI9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1103)

**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T-cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** p17 (84–92)

**Author Location** p17 (84–92)

**Epitope** TLYCVHQRI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** responses in children, mother-to-infant transmission

**References** Brander & Walker 1995

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

**HXB2 Location** p17 (84–92)

**Author Location** p17 (84–92)

**Epitope** TLYCVHQRI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

**HXB2 Location** p17 (84–92)

**Author Location** p17 (84–92)

**Epitope** TLYCVHQRI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p17 (84–92)

**Author Location** p17 (84–92 SF2)

**Epitope** TLYCVHQRI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 1/2 group 3.

**HXB2 Location** p17 (84–92)

**Author Location** p17 (84–92)

**Epitope** TLYCVHQRI

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** p17 (84–92)

**Author Location** Gag (Henan isolate)

**Epitope** VLYCVHQRI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (85–92)

**Author Location** p17

**Epitope** LYCVHQKI

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on a patient with an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p17 (86–96)

**Author Location** Gag (92–103)

**Epitope** YCVHAGIEVRD

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p17 (86–101)

**Author Location** p17 (SF2)

**Epitope** YCVHQRIEIKDTKEAL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

**HXB2 Location** p17 (86–101)

**Author Location** p17 (SF2)

**Epitope** YCVHQRIEIKDTKEAL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

**HXB2 Location** p17 (87–95)

**Author Location** Gag (Henan isolate)

**Epitope** CVHQRIEIK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (87–105)

**Author Location** p17 (91–105 SF2)

**Epitope** CRIDVKDTKEALEKIE

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** p17 (88–115)

**Author Location** p17 (88–115 ARV)

**Epitope** VHQRIEIKDTKEALDKIEEQNKSKKKA

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Achour *et al.* 1990

- B cell epitope HGP-30 also serves as a CTL epitope.

**HXB2 Location** p17 (88–115)

**Author Location** p17 (88–115 ARV)

- Epitope** VHQRIEIKDTKEALDKIEEEQNKSKKKA  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* CD4BS, HPG30, V3 *Adjuvant:* IL-12
- Species (MHC)** mouse (H-2<sup>d</sup>)  
**References** Hamajima *et al.* 1997
- B cell epitope HGP-30 also serves as a CTL epitope.
  - Vaccine combined HGP-30, V3 loop peptide variants, and CD4 binding site peptide.
  - IL-12 expression plasmid included with the vaccination enhanced the CTL response.
- HXB2 Location** p17 (89–98)  
**Author Location** Gag (Henan isolate)  
**Epitope** HQRIEIKDTK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006
  - CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (91–101)  
**Author Location** p17 (SF2)  
**Epitope** RIDVKDTKEAL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons, immunodominance  
**References** Goulder *et al.* 2000a
  - The CTL-dominant response was focused on this epitope in an HIV+ Haitian living in Boston, who was A23/68 B45/72 Cw2/16 – this epitope fell outside the most recognized peptides in the study.
  - Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
  - Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p17 (91–105)  
**Author Location** p17 (91–105 SF2)  
**Epitope** RIDVKDTKEALEKIE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A3, A24, B8, B55.

- HXB2 Location** p17 (92–101)  
**Author Location** p17 (92–101)  
**Epitope** IEIKDTKEAL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4001)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is a B\*4001 epitope.

- HXB2 Location** p17 (92–101)  
**Author Location** Gag (92–101)  
**Epitope** IDIKDTKEAL  
**Epitope name** IL10  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4001)  
**Donor MHC** A\*0201, A\*2402, B\*4001, B\*5001, Cw03, Cw04  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization  
**References** Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, IDIKDTKEAL (IL10) was restricted by HLA-B\*4001.

- HXB2 Location** p17 (92–101)  
**Author Location** p17  
**Epitope** IEIKDTKEAL  
**Epitope name** B40-IL10(p17)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B40)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
  - The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p17 (92–101)

**Author Location**

**Epitope** IEIKDTKEAL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B40)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p17 (92–101)

**Author Location** p17

**Epitope** IEIKDTKEAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**References** Wagner *et al.* 1998a

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1  $\alpha$  and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules.

**HXB2 Location** p17 (92–101)

**Author Location** p17 (92–101 SF2)

**Epitope** IEIKDTKEAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.

- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B60+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 1/1 group 2, and 0/0 group 3.

**HXB2 Location** p17 (92–101)

**Author Location** p17 (SF2)

**Epitope** IEIKDTKEAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes.
- B60 is present in 10-20% of the Caucoid and very common in Asian populations.

**HXB2 Location** p17 (92–101)

**Author Location** Gag (92–101)

**Epitope** IEIKDTKEAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Keywords** class I down-regulation by Nef

**References** Yang *et al.* 2002

- Nef down-modulates class I protein expression, and this study demonstrates directly that Nef-deleted HIV-1 NL-43 can be more effectively killed *in vitro* than NL-43 with an intact Nef. The effect was shown to be specific for class I presentation of epitopes, and unlike Nef, deleting Vpr did not alter CTL susceptibility of NL43 infected cells. The CTL clone 161JD27, specific for the class I B60 presented epitope IEIKDTKEAL, was one of four used in this study.

**HXB2 Location** p17 (92–101)

**Author Location** p17 (92–101 NL43)

**Epitope** IEIKDTKEAL

**Epitope name** IL10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Assay type** Chromium-release assay, CTL suppression of replication

**Keywords** escape

**References** Yang *et al.* 2003a

- Virus was cultured in the presence of CTL lines specific for 5 different epitopes (SLYNTVATL, ILKEPVHGV, IEIKDTKEAL, SEGATPQDL, and KEKGGLEGL) to study the emergence of escape mutations. Escape varied between clones for the same epitope, and between different epitopes. Gag and RT epitope escape, if it occurred at all, tended to be monoclonal and within the epitope, indicating strong fitness constraints, while the Nef epitope escape was rapid, polyclonal, and sometimes the result of upstream frameshifts.

- There was one cloned cell line that recognized IEIKDTKEAL, 161JD27. After 2 weeks of passaging HIV-1 in the presence of 161JD27, no mutations were observed within the epitope in 10 sequences; one of the 10 had a single E → K substitution 6 amino acids beyond the C-terminal end of the epitope.

**HXB2 Location** p17 (92–101)

**Author Location** Gag (92–101 B consensus)

**Epitope** IEIKDTKEAL

**Epitope name** IL10

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* adeno-associated virus (AAV)

*HIV component:* gp120

**Species (MHC)** human (B60)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** dynamics, immune evasion

**References** Brainard *et al.* 2004

- HIV-1 gp120 is shown to suppress the ability of antigen-specific CTLs to migrate or remain at sites of high viral replication by concentration-dependent chemotaxis and fugetaxis. Directional T-cell movement is shown to depend on the interaction of the V2 and V3 loops with the CXCR4 receptor. X4 HIV-1 gp120 causes the migration of T-cells, including HIV-1 specific CTL, away from infected target cells, another potential mechanism for immune evasion.

**HXB2 Location** p17 (92–101)

**Author Location** p17 (92–101)

**Epitope** IEIKDTKEAL

**Epitope name** Gag/p17-IL10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Assay type** Chromium-release assay

**Keywords** binding affinity, epitope processing, TCR usage, characterizing CD8+ T cells

**References** Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 1/14 CTL T-cell clones tested were specific for Gag/p17-IL10. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 value for the Gag/p17-IL10 clone was 8,000 pg/ml.

**HXB2 Location** p17 (92–101)

**Author Location** p17 (92–101)

**Epitope** IEIKDTKEAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60, B61)

**Keywords** immunodominance

**References** Day *et al.* 2001

- No immunodominant responses were detected to five B61-restricted epitopes tested.
- All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response.

**HXB2 Location** p17 (93–101)

**Author Location** p17 (93–101 B1 and B2)

**Epitope** EIKDTKEAL

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A03, A32, B08, B62, Cw3)

**Country** Netherlands

**Assay type** Other

**Keywords** subtype comparisons, computational epitope prediction, superinfection

**References** Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01\_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-B08 restricted epitope, EIKDTKEAL, varied to EvKDTKEAL in 83% of viruses in B1 within 4 years, dvKDTKEAL at the earliest time point taken in B2 with no changes over time, and EIIDTKEAL in AE at the earliest time point taken, with no changes over time. A reversion was seen in B1 to dIKDTKEAL i.e. v to I, suggesting a lack of CTL pressure on this sequence.

**HXB2 Location** p17 (93–101)

**Author Location** Gag (93–101)

**Epitope** EVKDTKEAL

**Epitope name** EL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*08)

**Donor MHC** A\*01, A\*02

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses

detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

- A minor response was detected against an E93D variant of this epitope, dVKDTKEAL. However, CTL responses effectively eliminated cells with this viral variant. Upstream of this epitope, EVKDTKEAL, an R91G mutation was seen that is suggested to affect processing of this EL9 epitope, such that this mutant viral population evaded immune responses restricted by HLAs A\*01, A\*02 and B\*08. Other variants detected were EiKDTKEAL, kVKDTKEAL and EVKDTKgAL.

**HXB2 Location** p17 (93–101)

**Author Location** Gag (99–107 WEAU)

**Epitope** EVKDTKEAL

**Epitope name** Gag EVL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Donor MHC** A\*2902, B\*0801, B\*4403

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, immunodominance, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- There was a weak response to this epitope during acute and early infection, and the epitope sequence did not vary during the first year of the infection.

**HXB2 Location** p17 (93–101)

**Author Location** p17

**Epitope** EVKDTKEAL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Donor MHC** A\*0101, A\*0301, B\*0801, B\*5101; A\*0101, B\*0801

**Country** United Kingdom

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** escape, acute/early infection, variant cross-recognition or cross-neutralization

**References** Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- The second donor in the study shares A\*0101 and B\*0801 with his partner. The epitope EVKDTKEAL has an escape variant in the donor that does not react in an Elispot assay, DvkGtkeal, but the Dvkdtkcal form was the transmitted variant. The transmitted form and EVKDTKEAL bind with equal affinity to B\*0801.
- The recipient mounted a response to the Dvkdtkcal form of the epitope. The variant DvRdtkeal was detected by 32 weeks post infection.

**HXB2 Location** p17 (93–101)

**Author Location** p17 (93–101)

**Epitope** EIKDTKEAL

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B8)

**References** DiBrino *et al.* 1994b

- Examined in the context of motifs important for HLA-B8 binding, predicted epitope based on Achour *et al.*

**HXB2 Location** p17 (93–101)

**Author Location** p17 (93–101)

**Epitope** EIKDTKEAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

**HXB2 Location** p17 (93–101)

**Author Location** p17 (93–101 LAI)

**Epitope** EIKDTKEAL

**Subtype** B

**Immunogen**

**Species (MHC)** human (B60, B8)

**References** Brander & Walker 1997

- Pers. comm. from A. Trocha and S. Kalams to C. Brander and B. Walker.

**HXB2 Location** p17 (93–101)

**Author Location** p17 (SF2)

**Epitope** DVKDTKEAL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ Caucasian from Boston, who was A1/\*0201 B8/63 Cw7/- – this epitope fell outside the most recognized peptides in the study.

- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNMLNTVVG (p24 41-60), and WEKIRLRPGGKKKYK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNMLNTVVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p17 (103–112)  
**Author Location** Gag (Henan isolate)  
**Epitope** KIEEEQNKSK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p17 (119–127)  
**Author Location** Gag (119–127 BORI)  
**Epitope** AADTGNSSQ  
**Epitope name** Gag AQ9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*2902, B\*1402, Cw\*0802  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** dynamics, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion  
**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.

- 20 variants in the AADTGNSSQ epitope were found in the patient BORI, the first appearing at day 35 with new variants continuing to arise through day 556. This is an extremely variable epitope, and changed not only by base substitution but by insertion and deletion. All variants tested conferred escape, at high concentrations of peptide.

**HXB2 Location** p17 (119–127)  
**Author Location** p17 (119–127)  
**Epitope** AADTGNSSQ  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*2902, B\*1402  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** HAART, ART, escape, viral fitness and reversion  
**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, AADTGNSSQ, was found to be 0.119/day, with SE of 0.021.
- A number of mutations in this epitope (Gag AQ9) abolished recognition completely. Gag AQ9 overlapped with a second epitope (Gag NP10), and a number of mutations conferring escape from the AQ9 directed response were shown to confer escape from NP10 responses as well. This will lead to an overestimate of the importance of a single CTL response. Escape at NP10 was not quantified separately on the grounds that it was insufficiently independent from escape at AQ9.

**HXB2 Location** p17 (121–132)  
**Author Location** p17 (121–132 HXB2R)  
**Epitope** DTGHSNQVSQNY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A33)  
**References** Buseyne *et al.* 1993b

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people.

**HXB2 Location** p17 (121–132)  
**Author Location** Gag (121–132 LAI)  
**Epitope** DTGHSNQVSQNY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A33)

**References** Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM17 (CDC P2A+C+D2) had a CTL response to two epitopes in Gag.

**HXB2 Location** p17 (123–132)**Author Location** Gag**Epitope** GNSSQVSQNY**Epitope name** GY10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A28, A29, B14, B44, Cw8**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 2, gKssqvsqny, was found not to correspond to the most polymorphic residues in the epitope. This is a novel partially mapped epitope.

**HXB2 Location** p17 (124–132)**Author Location** p17 (124–132 LAI)**Epitope** NSSKVSQNY**Subtype** B**Immunogen** HIV-1 or HIV-2 infection**Species (MHC)** human (B\*3501)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- Noted by Brander to be B\*3501 epitope.

**HXB2 Location** p17 (124–132)**Author Location** p17**Epitope** NSSQVSQNY**Immunogen** HIV-1 infection**Species (MHC)** human (B\*3501)**Keywords** binding affinity**References** Dorrell *et al.* 2001

- The crystal structure of this epitope bound to HLA-B\*3501 shows that a serine can fit into the B pocket, which is shared between B35 and B53, with the hydroxyl group of the P2 serine occupying a position almost identical to the P2 proline that was previously considered the anchor motif.
- Novel B53 epitopes (DTINEEAAEW and QATQEVKNNM) were defined in this study that showed that A and T can also serve as P2 anchor residues for the B pocket of HLA-B35 and B53 – while S, T, and P could all fit into the B pocket and

form a hydrogen bond, A would not form a bond, so the authors propose compensatory interactions account for the high affinity of QATQEVKNNM for B53.

**HXB2 Location** p17 (124–132)**Author Location** p17 (124–132 LAI)**Epitope** NSSKVSQNY**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Keywords** review**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.

**HXB2 Location** p17 (124–132)**Author Location****Epitope** NSSKVSQNY**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Keywords** dynamics, acute/early infection**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWILLGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGIEY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** p17 (124–132)**Author Location** p17 (124–132)**Epitope** NSSKVSQNY**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**References** Birk *et al.* 1998b

- A study of p17 variation considering known p17 epitopes and individuals with known HLA types revealed that p17 evolution is influenced by immune pressure from CTLs.

**HXB2 Location** p17 (124–132)**Author Location** p17 (124–132 LAI)**Epitope** NSSKVSQNY**Subtype** B**Immunogen** HIV-1 or HIV-2 infection



**Species (MHC)** human (B35)  
**Country** Gambia  
**Keywords** HIV exposed persistently seronegative (HEPS), HIV-2  
**References** Rowland-Jones *et al.* 1995

- Established by titration. HIV-1-infected and HIV-2-infected B35+ subjects recognized both the HIV-1 (NSSKVSQNY) and HIV-2 forms (PPSGKGGNY).

**HXB2 Location** p17 (124–132)  
**Author Location** p17 (124–132 LAI)  
**Epitope** NSSKVSQNY  
**Subtype** B  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (B35)  
**References** Lalvani *et al.* 1997

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers.
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors.

**HXB2 Location** p17 (124–132)  
**Author Location** p17  
**Epitope** NSSKVSQNY  
**Immunogen**  
**Species (MHC)** human (B35)  
**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive.
- HIV-2 version of this epitope is not conserved: PPSGKGGNY, but the CTLs are cross-reactive – this is one of five B35 CTL epitopes that are cross-reactive, see also Rowland-Jones *et al.* [1995].

**HXB2 Location** p17 (124–132)  
**Author Location** p17  
**Epitope** NSSKVSQNY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Keywords** HAART, ART  
**References** Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.

**HXB2 Location** p17 (124–132)  
**Author Location** p17 (124–132 SF2)  
**Epitope** NSSKVSQNY  
**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 0/2 group 2, and 1/1 group 3.

**HXB2 Location** p17 (124–132)  
**Author Location**  
**Epitope** NSSKVSQNY  
**Epitope name** Gag-NY9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 1/21 (5%) recognized this epitope.

**HXB2 Location** p17 (124–132)  
**Author Location** p17 (124–132)  
**Epitope** NSSKVSQNY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2/9 patients recognized this epitope.

**HXB2 Location** p17 (124–132)  
**Author Location**  
**Epitope** NSSKVSQNY  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease  
**Species (MHC)** human (B35)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p17 (124–132)

**Author Location** p17 (124–132 LAI)

**Epitope** PPSGKGGNY

**Subtype** HIV-2

**Immunogen** HIV-1 or HIV-2 infection

**Species (MHC)** human (B35)

**Country** Gambia

**Keywords** HIV exposed persistently seronegative (HEPS), HIV-2

**References** Rowland-Jones *et al.* 1995

- Established by titration. HIV-1-infected and HIV-2-infected B35+ subjects recognized both the HIV-1 (NSSKVSQNY) and HIV-2 forms (PPSGKGGNY).

## II-B-2 Gag p17-p24 CTL/CD8+ epitopes

**HXB2 Location** p17-p24 (119–3)

**Author Location** p17-p24

**Epitope** AADTGNSSQVSQNYPIV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11, A25)

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved

peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This overlapping peptide, AADTGNSSQVSQNYPIV, was differentially targeted across ethnic groups and had an overall frequency of recognition of 2.7% - 0% AA, 15.4% C, 0% H, 0% WI (P value = 0.001).

**HXB2 Location** p17-p24 (124–1)

**Author Location** Gag (124–133 BORI)

**Epitope** NSSQVSQNY

**Epitope name** Gag NP10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*2902, B\*1402, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- 10 variants in the NSSQVSQNY epitope were found in the patient BORI, the first appearing at day 35, NgSQVSQNY, with new variants continuing to arise through day 556. This is an extremely variable epitope, and changed not only by base substitution but by insertion and deletion. All variants tested conferred some degree of escape by diminishing the CTL response.

**HXB2 Location** p17-p24 (125–3)

**Author Location** Gag (133–143)

**Epitope** GKKVSQNYPIV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

- Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay
- Keywords** subtype comparisons
- References** Kaushik *et al.* 2005
- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
  - 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.
- HXB2 Location** p17-p24 (126–11)
- Author Location** (C consensus)
- Epitope** GKVSQNYPIVQNLQGQMV
- Subtype** C
- Immunogen** HIV-1 infection
- Species (MHC)** human (B13)
- Country** South Africa
- Assay type** CD8 T-cell Elispot - IFN $\gamma$
- Keywords** rate of progression
- References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HXB2 Location** p17-p24 (126–11)
- Author Location** Gag
- Epitope** SQVSQNYPIVQNLQGQMV
- Epitope name** GAG-03
- Subtype** B
- Immunogen** HIV-1 infection
- Species (MHC)** human
- Country** China
- Assay type** CD8 T-cell Elispot - IFN $\gamma$
- Keywords** subtype comparisons, immunodominance
- References** Zhao *et al.* 2007
- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
  - 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
  - Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
  - This peptide, EKIRLRPGGKKkYrLKHL differs from the consensus C sequence KIRLRPGGKKhYmLKHL at 2 amino acid positions, i.e. by 11.1%.
- HXB2 Location** p17-p24 (127–3)
- Author Location** p17-p24 (127–135 subtype D)
- Epitope** QVSQNYPIV
- Subtype** D
- Immunogen**
- Species (MHC)** human (A\*6802)
- References** Dong 1998
- Epitope starts in p17 and ends in p24.
  - Predicted on binding motif, no truncations analyzed.
- HXB2 Location** p17-p24 (127–3)
- Author Location** p17
- Epitope** QVSQNYPIV
- Epitope name** A68-QV9(p17)
- Immunogen** HIV-1 infection
- Species (MHC)** human (A68)
- Assay type** CD8 T-cell Elispot - IFN $\gamma$
- Keywords** rate of progression, immunodominance, early-expressed proteins
- References** Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
  - The most frequently recognised epitopes also elicited the greatest CTL response.
  - HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
  - HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
  - In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.
- HXB2 Location** p17-p24 (127–3)
- Author Location** p17
- Epitope** QVSQNYPIV
- Epitope name** A68-QV9
- Subtype** B
- Immunogen** HIV-1 infection
- Species (MHC)** human (A68)
- Donor MHC** A2, A68, B14, B44, Cw5, Cw8
- Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay
- Keywords** rate of progression, escape, acute/early infection, antibody generation, co-receptor, immune evasion
- References** Streeck *et al.* 2007b

- A subject with acute and rapid disease progression to AIDS showed no neutralizing antibody activity and rapid decline in HIV-specific CTL response by 6 months post-infection. Virus from this rapid progressor was resistant to neutralization by plasma from a long-term progressor. Viral epitopes did not vary much. This suggests viral immune evasion in the absence of viral sequence variation.
- This epitope, QVSQNYPIV, elicited a sub-dominant CTL response, not detectable after 6 months post-infection. QV9 and its flanking sequences NSSQVSQNYPIVQNL showed one escape mutation in the flanking sequence to sSSQVSQNYPIVQNL by 6 months post-infection.

**HXB2 Location** p17-p24 (129–7)

**Author Location** Gag (129–139)

**Epitope** SQNYPIVQNIQ

**Epitope name** Gag 7.3

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade  
*HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu

**Species (MHC)** macaque

**Assay type** T-cell Elispot, Intracellular cytokine staining

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization, memory cells

**References** Amara *et al.* 2005

- A clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better conserved for CD8 than CD4 T cells.
- All 5 CD8 and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation of a CD8 T cell epitope previously reported for humans as NYPIVQNL. HLA restriction: A\*2402.
- The response elicited to the B clade epitope SQNYPIVQNIQ does not cross-react with the CRF02 form SQNYPIVQNaQ. Other clades either most commonly carry an A or L in this position, SQNYPIVQN[a/l]Q.

**HXB2 Location** p17-p24 (131–6)

**Author Location** p17-p24 (132–140 SF2)

**Epitope** NYPIVQNL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**References** Ikeda-Moore *et al.* 1997

- The epitope starts in p17 and ends in p24.
- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- NYPIVQNL bound to A\*2402 with medium strength, and the epitope can be processed in a vaccinia construct and presented – no CTL clone was obtained.

## II-B-3 Gag p24 CTL/CD8+ epitopes

**HXB2 Location** p24 (3–11)

**Author Location** Gag (135–143)

**Epitope** VQNLQGQMV

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*13)

**Donor MHC** A\*0301, A\*3001, B\*1301, B\*1402, Cw\*0602, Cw\*0802

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism

**References** Honeyborne *et al.* 2007

- To determine whether HLA-B\*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B\*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B\*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.
- Variants of this epitope, VQNLQGQMV, were seen at positions 4, 7 and 9. A closer look at sequences just upstream and downstream of the optimal epitope, QNPVQNLQGQMVHQaiSPRTLNAWVKVEE, show that residues 146 and 147 show most change. In association with HLA-B\*57/5801, the epitope ISPRTLNAW (Gag, 147-155) may vary; whilst the HLA-B\*1510-restricted epitope VHQAIISPRTL (Gag, 143-152) varies at A146P to VHQpISPRTL. Such mutations may be seen  $\geq$  4 residues downstream of the epitope C terminus.

**HXB2 Location** p24 (3–11)

**Author Location**

**Epitope** VQNLQGQMV

**Epitope name** VV9

**Immunogen**

**Species (MHC)** human (B13)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B13 epitope.

**HXB2 Location** p24 (8–17)

**Author Location** Gag (140–149)

**Epitope** GQMVHQAIISP

**Subtype** A, C, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5802)

**Country** Tanzania

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, immunodominance

**References** Geldmacher *et al.* 2007a

- To assess whether T-cell specific responses to Gag and Nef are biased towards infecting subtype recombination, 56 ART-naive subjects were studied using six overlapping peptide sets consisting 15-mer peptides, covering both proteins completely. A multi-region hybridization assay was employed. Overall, the best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants GQMVHQaiSP, GQMVHQslSP and GQMVHQalSP were studied as peptide sequences GQMVHQaiSP-RTLNA (subtypes C and D), NLQ-GQMVHQslSP-RT (subtype A) and NAQ-GQMVHQalSP-RT with 16% responders. Frame-of-epitope effects prevented conclusions about such point mutations, but subtype C was best recognized.

**HXB2 Location** p24 (8–17)

**Author Location** p24 (140–149)

**Epitope** GQMVHQAIISP

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A\*0201, A1, B57 and responded to four B57 epitopes and two others.

**HXB2 Location** p24 (8–20)

**Author Location** p24 (140–152 IIIB)

**Epitope** GQMVHQAIISPRTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw3)

**References** Littau *et al.* 1991

- Fine specificity of human Cw3 restricted Gag CTL epitope.

**HXB2 Location** p24 (8–20)

**Author Location** p24 (8–20)

**Epitope** GQMVHQAIISPRTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw3)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.

- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** p24 (8–21)

**Author Location** p24 (8–21 B1 and B2)

**Epitope** GQMVHQAIISPRTLN

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A03, A32, B08, B62, Cw3)

**Country** Netherlands

**Assay type** Other

**Keywords** subtype comparisons, computational epitope prediction, superinfection

**References** Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01\_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-A03-supertype Cw3 restricted epitope, GQMVHQAIISPRTLN, varied to GQMVHQpISPRTLN in B1, GQMVHQpISPRTLN in B2 and GQMVHQpvSPRTLN in AE by the earliest time point taken, with no changes over time.

**HXB2 Location** p24 (8–27)

**Author Location** p24 (140–159)

**Epitope** GQMVHQAIISPRTLNAWVKVV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Musey *et al.* 1997

- CTL specific for this epitope were found in the peripheral blood but not in the cervical mucosa of one donor.

**HXB2 Location** p24 (9–18)

**Author Location** Gag (173–182)

**Epitope** QMVHQAIISPR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

- HXB2 Location** p24 (9–23)  
**Author Location** p24 (16–24)  
**Epitope** QMVHQSLSPRTLNAW  
**Subtype** A, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*3002, A\*6801, B\*5703, B\*5802;  
 A\*3001, A\*6601, B\*5801, B\*5802  
**Country** Uganda  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, variant cross-  
 recognition or cross-neutralization  
**References** Barugahare *et al.* 2005
- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
  - The sequence contains a known B7/B8 epitope, but the subjects recognizing it are B7- and B8-negative. The viral sequences isolated from the subjects were qmThqNlsprtlaw and qmvhqAlsprtlaw, and the peptide was recognized.

- HXB2 Location** p24 (10–18)  
**Author Location** Gag (144–152 SF2)  
**Epitope** MVHQAI SPR  
**Subtype** B  
**Immunogen** HIV-1 infection, computer prediction  
**Species (MHC)** human (A\*3303)  
**Assay type** Chromium-release assay  
**Keywords** binding affinity, computational epitope prediction  
**References** Hossain *et al.* 2003
- HLA-A\*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A\*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A\*3303. Six of these served as peptide-targets for lysis by PBMC from infected individual, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
  - This epitope is one of the 4 that are properly processed.

- HXB2 Location** p24 (10–18)  
**Author Location** Gag (174–182)  
**Epitope** MVHQAI SPR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3 supertype)  
**Keywords** supertype, rate of progression  
**References** Propato *et al.* 2001
- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
  - Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.

- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 5/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

- HXB2 Location** p24 (11–20)  
**Author Location** (C consensus)  
**Epitope** VHQAISPRTL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1510)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004
- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
  - This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

- HXB2 Location** p24 (11–20)  
**Author Location** (C consensus)  
**Epitope** VHQAISPRTL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1510)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - VHQAISPRTL is an optimal epitope.

- HXB2 Location** p24 (11–24)  
**Author Location** p24 (SF2)  
**Epitope** VQHAISPRTLNAW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons, immunodominance  
**References** Goulder *et al.* 2000a
- The CTL-dominant response was focused on this epitope in an HIV+ Haitian living in Boston, who was A34/68 B57/71 Cw3/7 – this epitope fell outside the most recognized peptides in the study.

- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNMLNTVVG (p24 41-60), and WEKIRLRPGGKKKYKLLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNMLNTVVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (11–25)

**Author Location** p24 (11–25 HXB2)

**Epitope** VHQAISPRTLNAWVK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 29% of the study subjects, and it was the third most frequently recognized peptide.

**HXB2 Location** p24 (11–32)

**Author Location** p24 (143–164 BH10)

**Epitope** VHQAISPRTLNAWVKVVEEKAF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

**HXB2 Location** p24 (12–20)

**Author Location**

**Epitope** HQAISPRTL

**Immunogen**

**Species (MHC)** human (B\*1510)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B\*1510 epitope.

**HXB2 Location** p24 (12–20)

**Author Location** Gag (146–154)

**Epitope** HQAISPRTL

**Immunogen** HIV-1 infection

**Species (MHC)** chimpanzee (Patr-B\*02)

**References** Balla-Jhaghoorsingh *et al.* 1999b

- Certain HLA-alleles have been associated with long-term survival – among them are HLA-B\*27 and HLA-B\*57.
- Of more than 150 chimpanzees that have been reported to be infected with HIV-1, only one has developed AIDS.
- CTL responses were studied in two HIV-1 infected chimpanzees that have strong CTL responses, and they were found to respond to highly conserved epitopes that are recognized in humans in the context of HLA-B\*27 and HLA-B\*57.
- The human HLA protein which presents this Patr-B\*02 epitope is HLA-B\*5701 but the amino acid sequences in the binding pockets of HLA-B\*5701 and Patr-B\*02 are distinctive.

**HXB2 Location** p24 (13–20)

**Author Location** p24 (145–152)

**Epitope** QAISPRTL

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (Cw3)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** p24 (13–23)

**Author Location** p24 (145–155 LAI)

**Epitope** QAISPRTLNAW

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*2501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an A\*2501 epitope.

**HXB2 Location** p24 (13–23)

**Author Location** p24 (13–23 HXB2)

**Epitope** QAISPRTLNAW

**Epitope name** QW11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2501)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Amino acid site in the third position potentially experienced positive selection. QAISPRTLNAW CTL escape mutant was found.

**HXB2 Location** p24 (13–23)  
**Author Location** p24 (145–155 LAI)  
**Epitope** QAISPRTLNAW  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (A25)  
**References** Kurane & West 1998

**HXB2 Location** p24 (13–23)  
**Author Location** p24 (145–155 SF2)  
**Epitope** QAISPRTLNAW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A25)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A25+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/2 group 2, and 1/3 group 3.

**HXB2 Location** p24 (13–23)  
**Author Location** Gag (145–155 IIIB)  
**Epitope** QAISPRTLNAW  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A25)  
**Assay type** Chromium-release assay  
**References** Kurane *et al.* 2003

- Three CD8+ CTL cell clones were derived from 2 HIV-1 positive asymptomatic patients, and their epitope specificities and HLA presenting proteins were defined.

**HXB2 Location** p24 (13–23)  
**Author Location**  
**Epitope** QAISPRTLNAW

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A25)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** supertype, cross-presentation by different HLA

- References** Frahm *et al.* 2007
- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
  - Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 1 allele previously known to be associated (A25) and 5 additional alleles (A23, A68, B44, Cw04, Cw07).

**HXB2 Location** p24 (13–23)  
**Author Location** p24 (145–155)  
**Epitope** QAISPRTLNAW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** immunodominance  
**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A\*0201, A1, B57 and responded to QAISPRTLNAW noted previously to be A25.

**HXB2 Location** p24 (13–23)  
**Author Location**  
**Epitope** QAISPRTLNAW  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox prime with gp120 boost  
*Strain:* B clade LAI, B clade MN  
*HIV component:* Gag-Pol, gp120, gp41  
**Species (MHC)** human  
**Donor MHC** A\*0202, A\*8001; B\*1801, B\*5301  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes  
**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.



- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** p24 (14–23)  
**Author Location** Gag  
**Epitope** AISPRTLNAW  
**Epitope name** IW9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Two escape mutations, at positions 1 (A146P) and 2 (I147L), were found in the most polymorphic residue in the epitope. Both were shared between clades B and C. Both were significantly more variable in persons expressing HLA-B57.

**HXB2 Location** p24 (14–23)  
**Author Location** p24  
**Epitope** AISPRTLNAW  
**Subtype** B, C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57, B63)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, cross-presentation by different HLA, optimal epitope  
**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 30% of B63-positive subjects and 29% of B57/58-positive subjects.

**HXB2 Location** p24 (15–23)  
**Author Location** Gag  
**Epitope** ISPRTLNAW  
**Epitope name** IW9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*310102, A\*6603, B\*440302, B\*570301, Cw\*040101, Cw\*07)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other  
**Keywords** escape, viral fitness and reversion, drug resistance

#### References Bailey *et al.* 2007

- In this study the entire HIV-1 genome was analyzed before and after virologic escape for the first time and escape mutations were temporarily associated with an increased viremia in an otherwise B\*57-elite controller of viral load. It is suggested that HLA-B\*57-restricted CTL mutations were the major cause of escape because other multiple drug resistance mutations in Pol and RT (M184V and T215Y) did not result in a marked increase in viral replication capacity in vitro.
- CTLs detecting this Gag epitope, ISPRTLNAW, were detectable and levels remained unchanged over 20 months. Most clones developed an A-P mutation in the position preceding IW9 which is a well-characterized processing escape mutation.

**HXB2 Location** p24 (15–23)  
**Author Location** p24  
**Epitope** LSPRTLNAW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2002

- Neisseria gonorrhoea cervicitis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhoea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

**HXB2 Location** p24 (15–23)  
**Author Location** Gag  
**Epitope** ISPRTLNAW  
**Epitope name** IW9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape  
**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- There was nearly equivalent IFN- $\gamma$  response to [i/m]SPRTLNAW and to [i/l]SPRTLNAW in several subjects, compared to the wild type.

**HXB2 Location** p24 (15–23)  
**Author Location** p24 (15–23)  
**Epitope** ISPRTLNAW  
**Epitope name** IW9

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (B\*57)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** binding affinity, subtype comparisons, acute/early infection**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this epitope, IW9 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen with both C- and A-clades. Anchor residues are at positions 2 and 9; while the A-clade variant contains a change at position 1 to ISPRTLNAW.

**HXB2 Location** p24 (15–23)**Author Location** Gag (147–155)**Epitope** ISPRTLNAW**Epitope name** IW9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*57)**Country** United States**Assay type** Intracellular cytokine staining, Other**Keywords** rate of progression, escape, immune evasion**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- One patient showed an I147L mutation in the HLA-B57 restricted epitope ISPRTLNAW, to ISPRTLNAW.

**HXB2 Location** p24 (15–23)**Author Location** p24 (15–23)**Epitope** ISPRTLNAW**Epitope name** IW9**Immunogen** HIV-1 infection**Species (MHC)** human (B\*57)**Country** United Kingdom, Kenya**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** TCR usage, structure, characterizing CD8+ T cells**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.
- In addition, immunodominance of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFN-PEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** p24 (15–23)**Author Location** Gag (144–152)**Epitope** ISPRTLNAW**Subtype** A, C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*57, B\*58)**Country** Tanzania**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** subtype comparisons, immunodominance**References** Geldmacher *et al.* 2007a

- To assess whether T-cell specific responses to Gag and Nef are biased towards infecting subtype recombination, 56 ART-naive subjects were studied using six overlapping peptide sets consisting 15-mer peptides, covering both proteins completely. A multi-region hybridization assay was employed. Overall, the best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants iSPRTLNAW and ISPRTLNAW were studied as peptide sequences HQA-iSPRTLNAW-YKV (subtype C), QMVHQS-ISPRTLNAW and QMVHQA-ISPRTLNAW with 20% responders. Frame-of-epitope effects prevented conclusions about such point mutations, but subtypes A and D were best recognized.

**HXB2 Location** p24 (15–23)**Author Location** p24 (147–155 IIIB)**Epitope** ISPRTLNAW**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5701 epitope.

**HXB2 Location** p24 (15–23)**Author Location****Epitope** ISPRTLNAW**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701)**Keywords** rate of progression, immunodominance

**References** Migueles & Connors 2001

- HLA B\*5701 was found in a very high frequency in HIV-1 infected non-progressors, 11/13 (85%) versus 19/200 (9.5%) of progressors. Non-progressors tended to have an immune response that was highly focused on four p24 epitopes that were presented by B\*5701, ISPRTLNAW, KAFSPEVIPMF, TSTLQEIQGW, and QASQEVKNW.

**HXB2 Location** p24 (15–23)**Author Location****Epitope** ISPRTLNAW**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701)**Keywords** rate of progression, immunodominance**References** Migueles & Connors 2001

- CTL activity was monitored in 27 individuals, including 10 LTNP with an over-expression of HLA B\*5701 – these individuals have viral loads below the threshold of infection without therapy, and their immune response tends to be focused on peptides that contain B\*5701 epitopes ISPRTLNAW, KAFSPEVIPMF, TSTLQEIQGW, and QASQEVKNW.
- CTL responses are broader in B\*5701+ individuals with progressive viremia than those that control viremia.
- The HLA-A\*0201 SLYNTVATL epitope response was not as strong in individuals that carried both A2, B57.

**HXB2 Location** p24 (15–23)**Author Location****Epitope** ISPRTLNAW**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701)**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay**Keywords** rate of progression, escape**References** Migueles *et al.* 2003

- cDNA Gag sequences from a set of 17 HLA-B\*5701+ progressors and 10 LTNPs were obtained, and the variation in four p24 B\*5701 epitopes examined. Sequence variants were more common ( $p < 0.01$ ) in the epitopes in the progressors (median 3, range 1-7) than LTNPs (median 2, range 0-4).
- In general use of the autologous protein in a target cell did not diminish the overall CD8+ T-cell responses.

**HXB2 Location** p24 (15–23)**Author Location** p24**Epitope** ISPRTLNAW**Immunogen** peptide-HLA interaction**Species (MHC)** human (B\*5701)**Assay type** Tetramer binding**Keywords** binding affinity**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80

tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.

- This epitope, ISPRTLNAW (MHC Class I restriction, serotype Bw4Ile80) complexed with MHC B\*5701 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

**HXB2 Location** p24 (15–23)**Author Location** p24 (15–23)**Epitope** ISPRTLNAW**Epitope name** ISP**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells**References** Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B57-ISP, is very strongly associated with delayed progression to AIDS, and its natural variants were less efficiently cross-recognized. Its alanine-substituted variants were poorly cross-recognized.

**HXB2 Location** p24 (15–23)**Author Location** Gag (147–155 LAI)**Epitope** ISPRTLNAW**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701, B\*5801)**Keywords** rate of progression**References** Klein *et al.* 1998

- B57 has been associated with long-term non-progression in the Amsterdam cohort.
- The most pronounced CTL responses in HLA B\*5701 LTS were to RT and Gag.

**HXB2 Location** p24 (15–23)**Author Location** Gag**Epitope** LSPRTLNAW**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5703)**Country** Kenya**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization**References** Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRF-FKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequence QLSLSPRTLNAW is associated with HLA-B\*5703 and contains the epitope LSPRTLNAW.

**HXB2 Location** p24 (15–23)

**Author Location** p24 (15–23)

**Epitope** LSPRTLNAW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope LSPRTLNAW showed its greatest conservation at 60% to subtype A.

**HXB2 Location** p24 (15–23)

**Author Location** p24 (147–155)

**Epitope** ISPRTLNAW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for IFN $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A\*0201, A1, B57 and responded to four B57 epitopes and two others, but not SLYNTVATL.

**HXB2 Location** p24 (15–23)

**Author Location** Gag (SF2)

**Epitope** ISPRTLNAW

**Epitope name** IW9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** acute/early infection

**References** Goulder *et al.* 2001a

- This epitope elicited the second strongest CTL response in patient PI004 during acute infection, and maintained the response.
- Three CTL responses, to epitopes TSTLQEIQGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKR-WII, and FLKEKGGL were detectable at 5 months post-infection and beyond.

**HXB2 Location** p24 (15–23)

**Author Location** p24 (147–155)

**Epitope** ISPRTLNAW

**Epitope name** ISP

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** HAART, ART, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B57+.

**HXB2 Location** p24 (15–23)

**Author Location** p24 (15–23)

**Epitope** ISPRTLNAW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (15–23)

**Author Location** p24 (147–155 SF2)

**Epitope** ISPRTLNAW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.

- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 2/2 group 3.

**HXB2 Location** p24 (15–23)

**Author Location**

**Epitope** ISPRTLNAW

**Epitope name** Gag-IW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 2/5 (40%) recognized this epitope.
- Among HIV+ individuals who carried HLA B58, 0/4 (0%) recognized this epitope.

**HXB2 Location** p24 (15–23)

**Author Location**

**Epitope** ISPRTLNAW

**Epitope name** ISP

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** p24 (15–23)

**Author Location** Gag (147–155)

**Epitope** ISPRTLNAW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A28, A3, B53, B57; A31, B57, B7

**Assay type** Chromium-release assay

**Keywords** TCR usage, genital and mucosal immunity

**References** Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCR $\beta$  VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood and semen of one male subject, and blood and cervix of one female subject.
- From the male patient, six clones that recognized this epitope had three different patterns of TCR $\beta$  usage: 2 from the blood and 1 from the semen used V $\beta$ 6S2DJ2S2; 1 from the blood and 1 from the semen used V $\beta$ 6S2DJ1.1; and 1 from the semen used V $\beta$ 7S1DJ2.3.

- From the female patient, five clones that recognized this epitope had different TCR $\beta$  usage. Blood derived clones were V $\beta$ 6S7DJ2.7, V $\beta$ 6.4DJ2.3, and V $\beta$ 6S3DJ2.1. Cervix derived clones were V $\beta$ 6S3DJ1.4 and V $\beta$ 6S5DJ2.5.

**HXB2 Location** p24 (15–23)

**Author Location** Gag (147–155)

**Epitope** ISPRTLNAW

**Epitope name** ISW9

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** epitope processing, escape

**References** Draenert *et al.* 2004b

- The A146P mutation flanking the ISW9 epitope (PisprtlNAW) is positively selected in HLA-B57+ persons and it prevents trimming of the optimal epitope by the endoplasmic reticulum aminopeptidase I. The A146P processing escape mutation does not influence replicative capacity of the virus in vitro and is accumulated over time in the human population.

**HXB2 Location** p24 (15–23)

**Author Location** p24 (15–23)

**Epitope** ISPRTLNAW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/7 patients recognized this epitope.

**HXB2 Location** p24 (15–23)

**Author Location** (147–155 B consensus)

**Epitope** ISPRTLNAW

**Epitope name** IW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** characterizing CD8+ T cells

**References** Allen *et al.* 2004

- This study characterizes an escape mutation in a C-terminal flanking residue of the HLA-A3 gag p17 KK9 epitope that inhibits processing, and is embedded in the overlapping HLA-A3 RK9 epitope.

- The immune response was tracked in subject AC-38. The acute immunodominant response was to the B57 TW10 epitope; this response declined following viral escape (tsNIqeqigw) by day 64. The p17 KK9 and RK9 became immunodominant, but then declined as the escape mutation arose. IW9 is 1 of 3 other strong responses that persisted, along with 1 sub-dominant response.

**HXB2 Location** p24 (15–23)

**Author Location** p24

**Epitope** ISPRTLNAW

**Epitope name** ISW9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** review, epitope processing, escape

**References** Goulder & Watkins 2004

- This paper is a review of the role of CTL in HIV infection, and it uses the ISW9 epitope as an example of an epitope that escapes due to a mutation before the N-terminal end of the epitope. The insertion of a proline prevents the aminopeptidase ERAAP from cleaving the glutamine from the precursor, qPisrptlnaw, preventing processing of ISRPTLNAW.

**HXB2 Location** p24 (15–23)

**Author Location** Gag

**Epitope** ISPRTLNAW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, epitope processing, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Characteristic changes in B57 epitopes in B57+ people were mapped: ISPRTLNAW often has the substitution Lsprtlnaw, as well as the proximal A->P substitution Pisrptlnaw.

**HXB2 Location** p24 (15–23)

**Author Location** p24 (147–155)

**Epitope** ISPRTLNAW

**Epitope name** IW9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Ethiopia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization

**References** Currier *et al.* 2005

- Epitope sequence variation and CD8 T-cell responses were analyzed in C subtype infected HLA-B57-positive individuals from Ethiopia. KF11 was the immunodominant response.
- ISPRTLNAW had a variant ISPRTLNAW in 7/10 B57+ subjects, and 4/9 B57- subjects; 2 other variants were observed, but there was no apparent sequence selection in this epitope.

**HXB2 Location** p24 (15–23)

**Author Location** Gag (147–155)

**Epitope** LSPRTLNAW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Canada

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** mimics

**References** Mason *et al.* 2005

- CTL responses against the human IP-30 signal peptide sequence LLDVPTAAV were shown to be elicited by stimulation of PBMCs from HIV-1 infected individuals with HIV protease peptide 76-84, LVGPTPVNI. In vitro stimulation with HIV PR 76-84 or the IP-30 signal peptide was shown to activate a comparable population of cross-reactive effector cells. None of the peptides activated CTL in non-HIV-infected individuals. IP-30 signal peptide was shown to have lower avidity T-cell interactions than the HIV peptide.
- As a control, responses to A2-restricted HIV epitopes ALVEICTEM, EELRQHLLRW, and LSPRTLNAW were shown not to give IP-30 responses.

**HXB2 Location** p24 (15–23)

**Author Location** Gag (147–155)

**Epitope** ISPRTLNAW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A\*3001, A\*66, B\*4201, B\*5802, Cw\*0602, Cw\*1701; A\*66, A\*68, B\*57, B\*5802, Cw\*0602, Cw\*0701

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** epitope processing, responses in children, mother-to-infant transmission, escape, acute/early infection

**References** Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- ISPRTLNAW is the C consensus form of the epitope and was the autologous form in the mother, and was transmitted to her infant. By 33 weeks a new dominant form of the epitope had emerged in the infant, mSPRTLNAW, and two additional variants had arisen, one with a substitution proximal to the epitope, pISPRTLNAW, and ISPRTLNAW.

**HXB2 Location** p24 (15–23)

**Author Location** p24 (15–23)**Epitope** ISPRTLNAW**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** HAART, ART, escape, viral fitness and reversion**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate reversion rate for this epitope, ISPRTLNAW, was found to be -0.005/day with a SE of 0.
- An A14P substitution in the flanking region of this B57-restricted epitope prevented correct processing of the epitope and conferred CTL escape. On transfer of this variant to an HLA-B57- individual, the frequency of the escape mutant actually increased giving a negative reversion rate of -0.005/day. This is consistent with in vitro replication and competition assays as well as with the accumulation of this mutation in the population, suggesting that A14P does not carry a fitness cost.

**HXB2 Location** p24 (15–23)**Author Location****Epitope** ISPRTLNAW**Immunogen** HIV-1 infection, vaccine*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease**Species (MHC)** human (B57)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p24 (15–23)**Author Location** p24 (147–155 IIB)**Epitope** ISPRTLNAW**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5801, B57)**Keywords** rate of progression**References** Goulder *et al.* 1996b

- Five slow progressors made a response to this epitope, and in two it was the dominant response.
- Peptide defined on the basis of B\*5801 binding motif, yet not cross-restricted except at high concentrations.

**HXB2 Location** p24 (15–23)**Author Location** Gag**Epitope** ISPRTLNAW**Epitope name** ISW9**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5801, B57)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** epitope processing, responses in children, mother-to-infant transmission, escape**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- ISPRTLNAW was recognized more often in children than in adults, and was the most frequently recognized B57 epitope in children. Escape variants of this epitope arose in 2 children: an A->P change proximal to the epitope, pISPRTLNAW, and an I1L change, ISPRTLNAW. In both cases the mother carried AISPRTLNAW.

**HXB2 Location** p24 (15–23)**Author Location** p24 (subtype A)**Epitope** LSPRTLNAW**Subtype** A**Immunogen** HIV-1 exposed seronegative**Species (MHC)** human (B57, B58)**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNT-VATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** p24 (15–23)**Author Location** p24 (147–155)

**Epitope** LSPRTLNAW**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (B57, B58)**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance**References** Kaul *et al.* 2001a

- Variants (L/D)SPRTLNAW are specific for the A/B clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B57/B58 women, 4/6 HEPS and 14/17 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 2 of the 4/6 HEPS cases and in 7 of the 14/17 responsive HIV-1 infected women.

**HXB2 Location** p24 (15–23)**Author Location** p24**Epitope** ISPRTLNAW**Subtype** B, D**Immunogen** HIV-1 infection**Species (MHC)** human (B58)**Donor MHC** A23, A24, B35, B58, Cw4, Cw7**Country** Democratic Republic of the Congo**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, variant cross-recognition or cross-neutralization**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence had an IIL change, ISPRTLNAW.

**HXB2 Location** p24 (15–23)**Author Location****Epitope** ISPRTLNAW**Immunogen****Species (MHC)** human (B63)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes that this is an B63 epitope.

**HXB2 Location** p24 (15–23)**Author Location** Gag**Epitope** ISPRTLNAW**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0602)**Donor MHC** A1, A3, B57, B7, Cw6, Cw7**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- I->L (LspRTLNAW) is associated with HLA C\*0602.

**HXB2 Location** p24 (15–23)**Author Location****Epitope** LSPRTLNAW**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human**Keywords** HIV exposed persistently seronegative (HEPS)**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- ISPRTLNAW was consistently recognized by 1/22 HEPS sex worker controls (ML1250), and LSPRTLNAW was recognized by 2 additional HEPS sex worker controls (ML1693 and ML1589).

**HXB2 Location** p24 (16–24)**Author Location** p24 (148–156)**Epitope** SPRTLNAWV**Immunogen****Species (MHC)** human (B\*0702)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0702 epitope.
- Optimal peptide mapped by titration.

**HXB2 Location** p24 (16–24)**Author Location** p24 (16–24)**Epitope** SPRTLNAWV**Immunogen** HIV-1 infection**Species (MHC)** human (B\*0702)



**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** computational epitope prediction, vaccine-specific epitope characteristics, cross-presentation by different HLA

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, SPRTLNAWV, was predicted to be restricted by HLA B\*0702, B\*3501, B\*5102, B\*5103, B\*5301, B\*5401 and B\*5502 as well.

**HXB2 Location** p24 (16–24)

**Author Location**

**Epitope** SPRTLNAWV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B07)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B07), an additional HLA (B42) was statistically predicted to be associated with this epitope.

**HXB2 Location** p24 (16–24)

**Author Location** p24 (148–156)

**Epitope** SPRTLNAWV

**Immunogen**

**Species (MHC)** human (B7)

**References** Brander & Walker 1997

- Optimal peptide mapped by titration, pers. comm. from D. Lewinsohn to C. Brander and B. Walker.

**HXB2 Location** p24 (16–24)

**Author Location** p24 (148–156)

**Epitope** SPRTLNAWV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Brodie *et al.* 2000

- Study tracks and quantifies *in vivo* migration of neo-marked CD8 HIV-specific CTL.
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication.
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1alpha and MIP-1beta, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism.
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*.

**HXB2 Location** p24 (16–24)

**Author Location** p24 (148–156)

**Epitope** SPRTLNAWV

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (B7)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Subject ML 1203 started with CTL responses to A\*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A\*6802 ETAYFILKL which became dominant, B7 TPGPGVIRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.

**HXB2 Location** p24 (16–24)

**Author Location** p24 (16–24)

**Epitope** SPRTLNAWV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP).
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.

- An acute seroconverter homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

**HXB2 Location** p24 (16–24)

**Author Location**

**Epitope** SPRTLNAWV

**Epitope name** Gag-SW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B07, 1/9 (11%) recognized this epitope.
- Among HIV+ individuals who carried HLA B81, 1/6 (17%) recognized this epitope.

**HXB2 Location** p24 (16–24)

**Author Location** p24 (16–24)

**Epitope** SPRTLNAWV

**Epitope name** B7-SV9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/11 HLA-B7 positive individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 1/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** p24 (16–24)

**Author Location** p24 (16–24)

**Epitope** SPRTLNAWV

**Epitope name** B7-SV9 Gag

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response, but in this case the epitope did not vary.

**HXB2 Location** p24 (16–24)

**Author Location** p24 (148–156)

**Epitope** SPRTLNAWV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- None of seven patients responded to this peptide with GzB producing cells or IFN-gamma producing cells.
- The authors describe the epitope as SPRTLNNQWV – the double N's may be a typo or an unusual form of the epitope; it is atypical and may be why there was no response.

**HXB2 Location** p24 (16–24)

**Author Location** p24 (16–24)

**Epitope** SPRTLNAWV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

**HXB2 Location** p24 (16–24)

**Author Location** p24

**Epitope** SPRTLNAWV

**Epitope name** B7-SV9(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (16–24)

**Author Location** p24 (subtype B)

**Epitope** SPRTLNAWV

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B\*8101, B7)

**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNT-VATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** p24 (16–24)

**Author Location** Gag (subtype B)

**Epitope** SPRTLNAWV

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B\*8101, B7)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B, and D clade viruses.

**HXB2 Location** p24 (16–24)

**Author Location** p24

**Epitope** SPRTLNAWV

**Immunogen** HIV-1 infection

**Species (MHC)** chimpanzee

**References** Santra *et al.* 1999

- 3/4 animals displayed HIV-1 Gag-specific CTL activity.

- Effector cells from two chimpanzees were able to recognize epitopes also recognized by human HIV-1 Gag-specific CTL (SPRTLNAWV, HLA-B7, and DLNTMLNTV, HLA-B14)
- No chimpanzee CTL were detected to the following human HIV-1 specific Gag epitopes, although they were embedded within 20mer peptides that contained a reactive epitope: ISPRTLNAW, HLA-B57; KRWILGLNK, HLA-B27; and DRFYKTLRA, HLA-B14.

**HXB2 Location** p24 (18–26)

**Author Location** Gag (150–)

**Epitope** RTLNAWVKV

**Epitope name** Gag150

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* p24 Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder, and induced CTL responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.

**HXB2 Location** p24 (19–26)

**Author Location** Gag

**Epitope** TLNAWVKW

**Epitope name** T9V

**Immunogen** vaccine

*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140 $\Delta$ V3

**Species (MHC)** transgenic mouse (A\*0201)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells

**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** p24 (19–27)

**Author Location** p24 (151–159)

**Epitope** TLNAWVKVV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Keywords** HAART, ART, immunodominance

**References** Huang *et al.* 2000

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed.
- Increases in gamma interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-gamma-production ELISPOT.
- In 3/3 HLA-A\*02, -B\*27 subjects the immunodominant epitope was against HLA B\*27 Gag p24 epitope KRWIILGL, not A2 Gag epitopes.

**HXB2 Location** p24 (19–27)

**Author Location** p24 (151–159)

**Epitope** TLNAWVKVV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Keywords** HAART, ART

**References** Rinaldo *et al.* 2000

- Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that can persist after therapy and long periods of virus being below the level of detection.

**HXB2 Location** p24 (19–27)

**Author Location** Gag (151–159)

**Epitope** TLNAWVKVV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

**HXB2 Location** p24 (19–27)

**Author Location** (LAI)

**Epitope** TLNAWVKVV

**Epitope name** T9V

**Subtype** B

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other

**Species (MHC)** human, transgenic mouse (A\*02.01)

**Country** France

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other

**Keywords** computational epitope prediction, Th1

**References** Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQANPDKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQANPDKTILKALGPA, NKIVRMYSPTSILDIRQGPK.
- Epitope T9V was one of 2 CTL reporter epitopes in recombinant mouse invariant chain constructs used for readout in a penatmer staining assay.

**HXB2 Location** p24 (19–27)

**Author Location** p24 (19–27)

**Epitope** TLNAWVKVI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, TLNAWVKVI, was predicted to be restricted by A\*0201, A\*0202, A\*0203, A\*0204, A\*0206.

**HXB2 Location** p24 (19–27)  
**Author Location** p24 (151–159)  
**Epitope** TLNAWVKVV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Parker *et al.* 1992; Parker *et al.* 1994  
 • Study of sequence motifs preferred for peptide binding to class I HLA-A2.

**HXB2 Location** p24 (19–27)  
**Author Location** p24 (19–27)  
**Epitope** TLNAWVKVV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Ferrari *et al.* 2000  
 • One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (19–27)  
**Author Location** p24 (150–159)  
**Epitope** TLNAWVKVI  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (A2)  
**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2001a  
 • Variants TLNAWVKV(I/V) are A/B clade specific.  
 • ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** p24 (19–27)  
**Author Location** p24 (A02, A30, B4402, B15)  
**Epitope** TLNAWVKVV  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** HIV exposed persistently seronegative (HEPS), characterizing CD8+ T cells  
**References** Missale *et al.* 2004  
 • HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.  
 • This patient responded to 4/8 HIV epitopes tested in an IFN $\gamma$  Elispot assay or tetramer assay. Responses were detected to this peptide 8 and 28 weeks after exposure with Elispot, but not by tetramer binding.

**HXB2 Location** p24 (19–27)  
**Author Location** p24 (19–27 HXB2)  
**Epitope** TLNAWVKVI  
**Epitope name** 24D

**Subtype B**  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* multiple epitope immunogen *HIV component:* p17/p24 Gag, Pol *Adjuvant:* IL-12

**Species (MHC)** transgenic mouse (A2)  
**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** vaccine-specific epitope characteristics, vaccine antigen design  
**References** Bolesta *et al.* 2005

- Immunization of transgenic mice with a codon-optimized hGagp17p24-Polp51 DNA plasmid, consisting of clusters of highly conserved CTL epitopes presented by multiple MHC class I alleles, induced 2- to 5-fold higher CD8+ T-cell responses than the corresponding full-length proteins. The modified proteins had the ribosomal frameshift deleted, as well as the potentially immunosuppressive p15, and protease and integrase. This correlated with higher protection against challenge with Gag and Pol expressing recombinant vaccinia virus. Mice immunized with the hGagp17p24-Polp51 also showed an elevated level of type 1 cytokine production as well as an increased titer of p24- and RT-specific IgG2 antibody responses.
- This was 1 of 4 A2 gag/pol epitopes tested. Transgenic mice immunized with the deleted construct induced more potent EliSpot reactions to this epitope than those immunized with full length Gag/Pol.

**HXB2 Location** p24 (19–27)  
**Author Location** p24 (subtype B)  
**Epitope** TLNAWVKVV  
**Subtype B**

**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (A\*0202, A2)  
**Keywords** subtype comparisons  
**References** Rowland-Jones *et al.* 1998b  
 • HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.  
 • Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.  
 • Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.  
 • This epitope is conserved among A, B and D clade viruses.

**HXB2 Location** p24 (21–30)  
**Author Location** Gag (153–162 WEAU)  
**Epitope** NAWVKIEEK  
**Epitope name** Gag NK9  
**Subtype B**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*2902, B\*0801, B\*4403  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, immunodominance, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- There was a weak response to this epitope during acute and early infection, and the epitope sequence did not vary during the first year of the infection.

**HXB2 Location** p24 (21–31)

**Author Location** Gag (129–139)

**Epitope** NAWVKVVEEKA

**Epitope name** Gag 8.4

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade  
*HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu

**Species (MHC)** macaque

**Assay type** T-cell Elispot, Intracellular cytokine staining

**Keywords** subtype comparisons, memory cells

**References** Amara *et al.* 2005

- A clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better conserved for CD8 than CD4 T cells.
- All 5 CD8 and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. The similar reported human epitope in this case is NAWVKVVEEKAFSPEVIPMF, HLA restriction: A2, B21, B57.
- The B clade immune response to NAWVKVVEEKA gives a diminished response to the CRF02 variant NAWVKViEEKA, but does cross-react. The M group clades are about evenly split between the 2 variants.

**HXB2 Location** p24 (21–40)

**Author Location** Gag (153–172)

**Epitope** NAWVKVVEEKAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Brodie *et al.* 1999

- The ability of CTL effector cells was studied by expanding autologous HIV-1 Gag-specific CTL *in vitro*, and adoptively transferring them.

- The transferred CTLs migrated to the lymph nodes and transiently reduced circulating productively infected CD4+ T cells, showing that CTL move to appropriate target sites and mediate anti-viral effects.

**HXB2 Location** p24 (21–40)

**Author Location** p24 (153–172)

**Epitope** NAWVKVVEEKAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Brodie *et al.* 2000

- Study tracks and quantifies *in vivo* migration of neo-marked CD8+ HIV-specific CTL.
- Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication.
- The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1 $\beta$  and MIP-1 $\gamma$ , CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism.
- This study provides a methodology for tracking and studying antigen specific CTL *in vivo*.

**HXB2 Location** p24 (21–40)

**Author Location** p24 (153–172 SF2)

**Epitope** NAWVKVVEEKAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A2, -B21.

**HXB2 Location** p24 (21–40)

**Author Location** p24 (153–172 SF2)

**Epitope** NAWVKVVEEKAFSPEVIPMF

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP) *HIV component:* CD4BS, Gag, gp120, V3

**Species (MHC)** macaque

**References** Wagner *et al.* 1998b

- A VLP is a non-infectious virus-like particle self-assembled from HIV Pr55 gag – macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains Gag and Env specific CTL were stimulated in each case, and Ab response to gag and gp120 was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4 – despite the CTL and Ab response, immunized macaques were infected by intervenous challenge with SHIV chimeric challenge stock Wagner *et al.* [1998b]
- CTL specific for this epitope could be found both before and after SHIV challenge.

**HXB2 Location** p24 (21–42)

**Author Location** p24 (153–174 BH10)

**Epitope** NAWVKVVEEKAFSPEVIPMFSA

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**References** Johnson *et al.* 1991
- Gag CTL response studied in three individuals.
- HXB2 Location** p24 (24–32)  
**Author Location** (C consensus)  
**Epitope** VKVIEEKAF  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004
  - HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
  - This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (24–32)  
**Author Location** (C consensus)  
**Epitope** VKVIEEKAF  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
  - A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - VKVIEEKAF is an optimal epitope.

**HXB2 Location** p24 (24–32)  
**Author Location**  
**Epitope** VKVIEEKAF  
**Immunogen**  
**Species (MHC)** human (B\*1503)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
  - C. Brander notes that this is an B\*1503 epitope.

**HXB2 Location** p24 (24–32)  
**Author Location** p24  
**Epitope** VKVVEEKAF  
**Subtype** B, C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)

- Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, rate of progression, immunodominance  
**References** Frahm *et al.* 2006
- CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects inspite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
  - VKVVEEKAF of clade B is a potential HLA-B\*1503-restricted epitope, with epitope VKViEEKAF found in clade C.
- HXB2 Location** p24 (27–36)  
**Author Location** p24 (27–36)  
**Epitope** IEEKAFSPEV  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4006)  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, immunodominance  
**References** Thakar *et al.* 2005
  - PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
  - 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
  - 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
  - Epitope IEEKAFSPEV showed >60% conservation with subtype D.

**HXB2 Location** p24 (27–37)  
**Author Location** (C consensus)  
**Epitope** IEEKAFSPEVI  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4501)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
  - A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - IEEKAFSPEVI is an optimal epitope.

**HXB2 Location** p24 (28–36)  
**Author Location** p24  
**Epitope** EEKAFSPEV  
**Subtype** A  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4415)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Bird *et al.* 2002

- 5/233, (4 HIV-1 positive, 1 HEPS) (2.1%) Kenyan female sex workers carried the novel HLA allele B\*4415.
- Residues forming the B pocket of HLA B\*4415 were identical to HLA B\*4001, B\*4402 and B\*4403. These alleles preferred E, an acidic residue, at the P2 position.
- The amino acid residues forming the F pocket of allele B\*4415 were not correlated with other known HLA molecules, but analogy suggests a binding preference for small, neutral amino acids.
- Based on the binding motif  $\chi$ [DE]xxxxxx[VILA], 19 potential B\*4415 epitopes were identified, and 1/19 was reactive in an Elispot, EEKAFSPEV.

**HXB2 Location** p24 (28–36)  
**Author Location** p24 (28–36)  
**Epitope** EEKAFSPEV  
**Immunogen**  
**Species (MHC)** human (B\*4415)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** p24 (28–36)  
**Author Location** (C consensus)  
**Epitope** EEKAFSPEV  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4501)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (28–47)  
**Author Location** p24 (160–179)  
**Epitope** EEKAFSPEVPMFSALSEGA  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**References** Musey *et al.* 1997

- Cervical and peripheral blood derived CTL clones from an HIV-infected woman recognized this epitope.

**HXB2 Location** p24 (29–36)  
**Author Location** p24 (28–36)  
**Epitope** EKAFSPEV  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*0602)  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, immunodominance  
**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa. 2
- 6 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope EKAFSPEV showed conservation across all clades with 100% against subtypes B and Indian C.

**HXB2 Location** p24 (29–39)  
**Author Location** Gag (161–171)  
**Epitope** EKAFSPEVIPM  
**Epitope name** Gag 8.5  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade  
*HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu  
**Species (MHC)** macaque  
**Assay type** T-cell Elispot, Intracellular cytokine staining  
**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization, memory cells  
**References** Amara *et al.* 2005

- A clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better conserved for CD8 than CD4 T cells.
- All 5 CD8 and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. The similar reported human epitope in this case is EEKAFSPEVPMFSALSEGA, HLA restriction: B27
- This epitope is conserved in all HIV-1 clades except CRF01, and is identical in B and CRF02.

**HXB2 Location** p24 (29–48)  
**Author Location** Gag (161–180 C consensus)  
**Epitope** EKAFSPEVPMFTALSEGAT  
**Subtype** C



**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons  
**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** p24 (30–37)  
**Author Location** p24 (30–37)  
**Epitope** KAFSPEVI  
**Epitope name** K18  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Country** United Kingdom, Kenya  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** TCR usage, structure, characterizing CD8+ T cells  
**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.
- In addition, immunodominance of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** p24 (30–37)  
**Author Location** p24 (162–170 LAI)  
**Epitope** KAFSPEVI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5703)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5703 epitope.

**HXB2 Location** p24 (30–37)  
**Author Location** p24 (30–37)  
**Epitope** KAFSPEVI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**References** Goulder *et al.* 2000c

- Two strong clonal CTL responses were generated in donor 026-BMC (HLA A3/-, B42/B57, Cw7/17) against different optimal versions of this epitope, one 8 amino acids long, one 11.
- Improved stabilization of the B57-peptide complex was demonstrated by the 11 mer which fits the B57 binding motif, relative to the 8 mer, which does not.
- B57 tolerates marked difference in optimal peptide length – and B57 is associated with non-progressive infection.

**HXB2 Location** p24 (30–37)  
**Author Location**  
**Epitope** KAFSPEVI

**Epitope name** Gag-KI8  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**References** Sabbaj *et al.* 2003

- Among HIV+ individuals tested who carried HLA B57, 0/5 (0%) recognized this epitope.

**HXB2 Location** p24 (30–40)  
**Author Location**  
**Epitope** KAFSPEVIPMF  
**Epitope name** KF11  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*310102, A\*6603, B\*440302, B\*570301, Cw\*040101, Cw\*07)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other  
**Keywords** escape, viral fitness and reversion, drug resistance

**References** Bailey *et al.* 2007

- In this study the entire HIV-1 genome was analyzed before and after virologic escape for the first time and escape mutations were temporarily associated with an increased viremia in an otherwise B\*57-elite controller of viral load. It is suggested that HLA-B\*57-restricted CTL mutations were the major cause of escape because other multiple drug resistance mutations in Pol and RT (M184V and T215Y) did not result in a marked increase in viral replication capacity in vitro.
- CTLs detecting this Gag epitope, ISPRTLNAW, were detectable and levels remained unchanged over 20 months. No mutations developed in the KF11 epitope.

**HXB2 Location** p24 (30–40)  
**Author Location** p24  
**Epitope** KAFSPEVIPMF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Keywords** HAART, ART  
**References** Spiegel *et al.* 1999

- Study examines the effect of highly active antiretroviral therapy (HAART) on HIV-1 plasma viral load, CTLp and CTLf frequencies in 8 infected children.
- CTLp (precursors) were measured by stimulating in culture and assaying using <sup>51</sup>Cr release, against vaccinia expressed III B Env, Gag, Pol, Nef, and CTLf were measured by ELISPOT.
- CTL against B\*57-KAFSPEVIPMF was a de novo response observed in one of the children when viral load increased as a result of stopping therapy.
- HIV-1 specific CTL responses initially increased in children with complete viral suppression, but then decreased, suggesting viral replication is needed to maintain CTL responses.

**HXB2 Location** p24 (30–40)  
**Author Location** Gag  
**Epitope** KAFSPEVIPMF  
**Epitope name** KF11  
**Subtype** B, C

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding  
**Keywords** subtype comparisons, escape, viral fitness and reversion, optimal epitope  
**References** Leslie *et al.* 2005
- An escape mutation, A2G (KgFSPEVIPMF), is suggested to be a result of selection pressure from the HLA-B\*57 allele, and can be transmitted and stable in the absence of HLA-B\*57. Evidence indicated that the mechanism of escape was an increased off-rate.
- HXB2 Location** p24 (30–40)  
**Author Location** Gag  
**Epitope** KAFSPEVIPMF  
**Epitope name** KF11  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape  
**References** Bailey *et al.* 2006b
  - Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
  - A163S mutation in this epitope can potentially act as a CTL escape mutation.

**HXB2 Location** p24 (30–40)  
**Author Location** p24 (30–40)  
**Epitope** KAFSPEVIPMF  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** binding affinity, subtype comparisons, acute/early infection  
**References** Malhotra *et al.* 2007b
  - T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.

- This epitope, KAFSPEVIPMF, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences.

- HXB2 Location** p24 (30–40)  
**Author Location** p24 (30–40)  
**Epitope** KAFSPEVIPMF  
**Epitope name** KF11  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Assay type** CTL suppression of replication  
**Keywords** class I down-regulation by Nef  
**References** Adnan *et al.* 2006
- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
  - Late protein Gag epitope KAFSPEVIPMF-recognizing CTLs were less affected by Nef.

- HXB2 Location** p24 (30–40)  
**Author Location** Gag  
**Epitope** KAFSPEVIPMF  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** characterizing CD8+ T cells  
**References** Addo *et al.* 2007
- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.
  - B\*57-restricted epitope KAFSPEVIPMF does not correlate with any particular CTL maturation phenotype. No study subjects generated terminally differentiated CTLs against this epitope.

- HXB2 Location** p24 (30–40)  
**Author Location** p24 (162–172)  
**Epitope** KAFSPEVIPMF  
**Epitope name** KF11  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*08, B\*57)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** rate of progression, acute/early infection, memory cells

**References** Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope KF11, KAFSPEVIPMF, IFN-gamma was produced by CD127 lo cells by both controllers and chronic patients. IL-2 and TNF-alpha were produced by both CD127 hi and lo cells in controllers.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (162–172 LAI)

**Epitope** KAFSPEVIPMF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** rate of progression

**References** Goulder *et al.* 1996b

- This peptide was recognized by CTL from five slow progressors.
- Peptide defined on the basis of B\*5801 binding motif, yet not cross-restricted except at high concentrations.
- This epitope is highly conserved.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (162–172 LAI)

**Epitope** KAFSPEVIPMF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5701 epitope.

**HXB2 Location** p24 (30–40)

**Author Location**

**Epitope** KAFSPEVIPMF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** rate of progression, immunodominance

**References** Migueles & Connors 2001

- HLA B\*5701 was found in a very high frequency in HIV-1 infected non-progressors, 11/13 (85%) versus 19/200 (9.5%) of progressors. Non-progressors tended to have an immune response that was highly focused on four p24 epitopes that were presented by B\*5701, ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.
- Attempts to make all for HLA B\*5701-epitope tetramers were made, but only the HLA B\*5701-KAFSPEVIPMF tetramer folded properly. The percentage of CD8+ T cells staining with this HLA B\*57 gag tetramer and the fraction of CD69+IFN-γ cells responding to autologous B cells pulsed with KAFSPEVIPMF was highly correlated ( $r = 0.84$ ;  $P = 0.005$ ). The percent of CD8+ T cells that stain with the A\*2 gag SLYNTVATL tetramer was low (0–0.31%) in a A2+ B57+ LTNP, emphasizing the focus of the immune response on the B\*5701 epitopes.

**HXB2 Location** p24 (30–40)

**Author Location**

**Epitope** KAFSPEVIPMF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** rate of progression, immunodominance

**References** Migueles & Connors 2001

- CTL activity was monitored in 27 individuals, including 10 LTNP with an over-expression of HLA B\*5701 – these individuals have viral loads below the threshold of infection without therapy, and their immune response tends to be focused on peptides that contain B\*5701 epitopes ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.
- CTL responses are broader in B\*5701+ individuals with progressive viremia than those that control viremia.
- The HLA-A\*0201 SLYNTVATL epitope response was not as strong in individuals that carried both A2 and B57.

**HXB2 Location** p24 (30–40)

**Author Location** Gag (162–172)

**Epitope** KAFSPEVIPMF

**Epitope name** KAF11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Migueles *et al.* 2003

- cDNA Gag sequences from a set of 17 HLA-B\*5701+ progressors and 10 LTNPs were obtained, and the variation in four p24 B\*5701 epitopes examined. Sequence variants were more common ( $p < 0.01$ ) in the epitopes in the progressors (median 3, range 1–7) than LTNPs (median 2, range 0–4).
- In general, use of the autologous protein in a target cell did not diminish the overall CD8+ T-cell responses.
- This epitope tends to be quantitatively immunodominant in B57+ people, including in some of the individuals in this study. It was extremely well conserved in the sequences obtained here, despite strong immune pressure, suggesting fitness constraints.

**HXB2 Location** p24 (30–40)

**Author Location** p24

**Epitope** KAFSPEVIPMF

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B\*5701)

**Assay type** Tetramer binding

**Keywords** binding affinity

**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently

expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.

- This epitope, KAFSPEVIPMF (MHC Class I restriction, serotype Bw4Ile80) complexed with MHC B\*5701 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C. However, the complex B\*57-KAFSPEVIPMF does bind inhibitory KIR3DL1 subtype KIR3DL1\*005.

**HXB2 Location** p24 (30–40)

**Author Location** p24

**Epitope** KGFNPEVIPMF

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B\*5701)

**Assay type** Tetramer binding

**Keywords** binding affinity

**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, KGFNPEVIPMF (MHC Class I restriction, serotype Bw4Ile80) complexed with MHC B\*5701 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (30–40)

**Epitope** KAFSPEVIPMF

**Epitope name** KAF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, TCR usage, variant cross-recognition or cross-neutralization

**References** Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B57-KAF that is strongly associated with delayed progression to AIDS and its natural as well as alanine-substituted variants are efficiently cross-recognized. At lower peptide concentrations, efficiency of variant cross-recognition was reduced, even while interepitopic differences in variant cross-recognition efficiency were maintained. CTLs responding to this epitope expressed the same predominant TCR

Vbeta family, but individuals whose CTLs predominantly used TCR Vbeta 17 had less efficient variant cross-reactivity.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (30–40)

**Epitope** KAFSPEVIPMF

**Epitope name** KAFS

**Subtype** A, B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701, B\*5703)

**Keywords** subtype comparisons, rate of progression

**References** Gillespie *et al.* 2002

- CTL responses of eight HIV+ slow progressors from Nairobi Kenya or Oxford, UK who were B\*5701 or B\*5703 were studied, as B\*57 is associated with slow progression.
- This epitope is located between the structurally conserved alpha-helix 1 and alpha-helix 2 (H1-H2) region of the p24 capsid protein, and tends to elicit strong reactions in B\*57 individuals.
- Broad heterogeneous cross-clade reactivity to 6 clade variants of the KAFS peptide sequence were observed in one B\*5701 and 5 B\*5703 HLA-restricted patients, measured by IFN- $\gamma$  production Elispot assays as well as tetramer binding. The clade variants were: KAFSPEVIPMF (clades A and B), kGfNpevipmf (clades A/AC); kaLspevipmf (clade A); kafspevipVf (clade A); kafNpelipmf (group O); kafspeIipmf (A/C); kafsQevipmf (A/C); and kaLspevipmf KNFSPEVIPMF A/G). Not all variants were well recognized in all patients, for example kafsQevipmf was not able to induce IFN gamma production in 3/6 tested, and had a diminished capacity to sensitize target cells for lysis.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (30–40)

**Epitope** KAFSPEVIPMF

**Epitope name** KF11

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701, B\*5703)

**Country** United Kingdom, Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining

**Keywords** TCR usage, structure, characterizing CD8+ T cells

**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.
- KAFSPEVIPMF and variant KGFNPEVIPMF induce distinct functional responses in KAFSPEVIPMF and KGFNPEVIPMF specific T cells, while the structures of B\*57-peptide complexes are similar.

**HXB2 Location** p24 (30–40)

**Author Location** Gag

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701, B\*5703)

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization

**References** Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRF-FKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequences EKAFSPEVPMFSAL and EKgFnPEVPMF-SAL are associated with HLA-B\*5701/03 and contain the epitope KAFSPEVPMF (KF11). Variable cross-reactivity was seen between subjects with respect to the 2 sequence variants.

**HXB2 Location** p24 (30–40)

**Author Location** Gag

**Epitope** KAFSPEVPMF

**Epitope name** KF11

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701, B\*5703)

**Country** United Kingdom, India, United States, South Africa

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay, Other

**Keywords** subtype comparisons, escape, TCR usage, immune evasion

**References** Yu *et al.* 2007a

- To study the contributions of HLA alleles and TCRs to the prevention of viral escape, HLAs B\*5701 and B\*5703 that differ at only 2 residues were followed with epitope KF11 and variants. B\*5701-KF11 allowed fewer viral mutations along with a narrow TCR repertoire while B\*5703-KF11 had a greater repertoire of TCR but also greater numbers of escape mutations. Therefore extensive TCR diversity is not a prerequisite to the prevention of viral mutations. More heterogeneous TCR-beta chains were also seen in the HLA-B\*5703-KF11 situation and greater numbers of KF11 variants arose especially in clade C-infected subjects.
- For both Clades B and C HIV-1, this epitope KAFSPEVPMF (wt) i.e. KF11 spawned variants KgFSPEVPMF (A2G), KnFSPEVPMF (A2N), KsFSPEVPMF (A2S), KsFnPEVPMF (A2S-S4N) and KsFSPEiPMF (A2S-V7I). In addition, Clade C also allowed variants KgFnPEVPMF (A2G-S4(N/K)) and KgFkPEVPMF (A2G-S4(N/K)). Overall, HLA-B\*5703 subjects showed more of these sequence variants than HLA-B\*5701 possessing subjects did.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (162–172 LAI)

**Epitope** KAFSPEVPMF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5703)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5703 epitope.

**HXB2 Location** p24 (30–40)

**Author Location**

**Epitope** KAFSPEVPMF

**Epitope name** Gag-KF11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5703)

**Donor MHC** A\*3402, A\*7401, B\*0801, B\*5703, Cw\*0302, Cw\*0701

**Keywords** HAART, ART

**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 00RCH59 was African American, on HAART, viral load 170, CD4 count 477.
- Among HIV+ individuals who carried HLA-B57, 6/6 (100%) recognized this epitope.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (162–172)

**Epitope** KAFSPEVPMF

**Epitope name** KF11

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5703)

**Country** Ethiopia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, escape, variant cross-recognition or cross-neutralization

**References** Currier *et al.* 2005

- HLA-B57 is associated with slow progression. Epitope sequence variation and CD8 T-cell responses were analyzed in HLA-B\*5703-positive individuals from Ethiopia. KF11 epitope and its variants were found to be immunodominant in these subjects. Two HLA-B\*5702 subjects did not respond to the KF11 epitope or its variants.
- 5 variants of the epitope were observed: KAFSPEVPMF, KnFSPEVPMF, rAFSPEVPMF, KgFnPEVPMF, and KAFSPEVPMF. Depending on the subject, different versions of these variants were more or less susceptible to their CD8+ T cells, i.e., one person's escape form was another person's susceptible form.

**HXB2 Location** p24 (30–40)

**Author Location** (C consensus)

**Epitope** KAFSPEVPMF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5703)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the A2 and S4 residues of KAFSPEVIPMF are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** p24 (30–40)

**Author Location** Gag

**Epitope** KAFSPEVIPMF

**Epitope name** KF11

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5703)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** rate of progression, HLA associated polymorphism

**References** Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than "other" HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by "other", non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also showed lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- This Gag epitope KF11 is highly variant in the African cohort when restricted by B\*5703, but is conserved in the Caucasian B\*5701-positive cohort.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (30–40)

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Goulder *et al.* 2000c

- Two strong clonal CTL responses were generated in donor 026-BMC (HLA A3/–, B42/B57, Cw7/17) against different optimal versions of this epitope, one 8 amino acids long, one 11.
- Improved stabilization of the B57-peptide complex was demonstrated by the Imer which fits the B57 binding motif, relative to the 8 mer, which does not.

- B57 tolerates marked difference in optimal peptide length – and B57 is associated with non-progressive infection.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (162–172)

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for IFN $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A\*0201, A1, B57 and responded to four B57 epitopes and two others.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (SF2)

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ Caucasian living in Boston – this epitope is not among the most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRL-RPGGKKKYKLLK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (30–40)

**Author Location** Gag (SF2)

**Epitope** KAFSPEVIPMF

**Epitope name** KF11

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Goulder *et al.* 2001a

- Three CTL responses in patient PI004, to epitopes TSTLQE-QIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (162–172)

**Epitope** KAFSPEVIPMF

**Epitope name** KAF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** HAART, ART, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B57+.

**HXB2 Location** p24 (30–40)**Author Location** p24**Epitope** KAFSPEVPMF**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**References** Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.

**HXB2 Location** p24 (30–40)**Author Location** p24 (162–172 SF2)**Epitope** KAFSPEVPMF**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**Keywords** HAART, ART, acute/early infection**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 2/2 group 3.

**HXB2 Location** p24 (30–40)**Author Location** p24 (163–174)**Epitope** KAFSPEVPMF**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**References** Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$ .

**HXB2 Location** p24 (30–40)**Author Location****Epitope** KAFSPEVPMF**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 1/5 (20%) recognized this epitope.

**HXB2 Location** p24 (30–40)**Author Location** p24**Epitope** KAFSPEVPMF**Epitope name** KAF**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**Keywords** HAART, ART, supervised treatment interruptions (STI)**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** p24 (30–40)**Author Location** p24 (30–40)**Epitope** KAFSPEVPMF**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**Donor MHC** A\*0201, A3, B44, B57, Cw5, Cw6**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** acute/early infection, early-expressed proteins**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most

avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.

- All HIV-1 proteins except Vpu were recognized, and responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- Alleles A3, B35, B57, and B62 were more frequently recognized than alleles A1, A2, A30, and A44 e.g., during primary infection. 2/10 patients, 1372 and 1397, recognized A2-restricted epitopes. The common A2-restricted epitopes Gag SL9 and Pol IV9 were not recognized in peptide tetramer-binding assays.

**HXB2 Location** p24 (30–40)

**Author Location** p24

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** Intracellular cytokine staining

**Keywords** immunodominance, genital and mucosal immunity

**References** Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T-cell responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T-cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 10/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

**HXB2 Location** p24 (30–40)

**Author Location** p24 (163–174)

**Epitope** KAFSPEVIPMF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A\*0201, A3, B57, Cw\*06, Cw\*07; A\*01, A\*0201, B\*08, B\*57, Cw6, Cw7

**Country** United States

**Assay type** Cytokine production, Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization

**Keywords** TCR usage

**References** Betts *et al.* 2004

- Both cytokine production and degranulation in HIV-1 specific and CMV specific CD8+ T-cells occurs at high peptide concentrations together with TCR downregulation. Only degranulation is observed at lower peptide concentrations with no observed TCR downregulation. Thus the nature of CTL response depends not on the specific T cell clonotype or antigen, but on the concentration of Ag presented on APCs.

**HXB2 Location** p24 (30–40)

**Author Location** p24

**Epitope** KAFSPEVIPMF

**Epitope name** TW10

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** epitope processing, escape

**References** Draenert *et al.* 2004b

- This study characterizes the N-terminal flanking position of the epitope ISPRTLNAW, and mutations in this position are thought to impact processing. The B57 epitope KAFSPEVIPMF was used as a positive control in this study.

**HXB2 Location** p24 (30–40)

**Author Location** Gag (155–172 B con)

**Epitope** KAFSPEVIPMF

**Epitope name** KF11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** variant cross-recognition or cross-neutralization

**References** Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN EliSpot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
- 2 subjects recognized this epitope, 1 with high functional avidity, 1 with intermediate. Autologous sequence revealed no substitutions in this epitope compared to the B consensus.

**HXB2 Location** p24 (30–40)

**Author Location** Gag

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.



- 1/2 HLA B57+ infection-resistant men, compared to 0/1 pre-seroconversion men who went on to become infected, reacted to this epitope.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (30–40)

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 7/7 patients recognized this epitope.

**HXB2 Location** p24 (30–40)

**Author Location** (162–172 B consensus)

**Epitope** KAFSPEVIPMF

**Epitope name** KF11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** immunodominance, characterizing CD8+ T cells

**References** Allen *et al.* 2004

- This study characterizes an escape mutation in a C-terminal flanking residue of the HLA-A3 gag p17 KK9 epitope that inhibits processing, and is embedded in the overlapping HLA-A3 RK9 epitope.
- The immune response was tracked in subject AC-38. The acute immunodominant response was to the B57 TW10 epitope; this response declined following viral escape (tsNIqeqigw) by day 64. The p17 KK9 and RK9 became immunodominant, but then declined as the escape mutation arose. FK11 is 1 of 3 other strong responses that persisted, along with 1 sub-dominant response.

**HXB2 Location** p24 (30–40)

**Author Location** (C consensus)

**Epitope** KAFSPEVIPMF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (30–40)

**Author Location** p24

**Epitope** KAFSPEVIPMF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** United Kingdom

**Assay type** Tetramer binding, T-cell Elispot, Intracellular cytokine staining

**Keywords** rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction

**References** Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

**HXB2 Location** p24 (30–40)

**Author Location** Gag

**Epitope** KAFSPEVIPMF

**Epitope name** KF11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was quite conserved in people carrying B57, but two substitutions were found in 11 B57+ individuals tested: kNfspevipmf and kafspelipmf.

**HXB2 Location** p24 (30–40)

**Author Location** Gag (162–172)

**Epitope** KAFSPEVIPMF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** p24 (30–40)

**Author Location** Gag (162–172 BRU)

**Epitope** KAFSPEVIPMF

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 1/9 CRF02\_AG-infected Ivoirians, and 1/9 B-infected French subjects.

**HXB2 Location** p24 (30–40)

**Author Location** Gag

**Epitope** KAFSPEVIPMF

**Epitope name** KAF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Netherlands

**Assay type** Tetramer binding, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, rate of progression, escape, characterizing CD8+ T cells

**References** Jansen *et al.* 2005

- HLA-B57 has been associated with long term non-progression in HIV+ people. The number and responsiveness of CD8 T-cells directed to different Gag peptides presented by HLA-A2, -B8 and B57 were compared. T cells specific for the HLA-B57 epitope KAFSPEVIPMF responded to a higher extent and more readily to antigenic stimulation than those specific for the A2 epitope SLYNTVATL and the B8 epitope EIYKRWII.
- Tetramer decay experiments indicate that the HLA-B57 peptide has a higher half-life than the A2 and B8 peptides. The authors point out that CD8+ T cells with high binding affinity may require less help.
- Variant forms of the HLA-B57 epitope KAFSPEVIPMF were found in the 3/5 HLA B57+ individuals sequenced, but the variants were always a minor form.

**HXB2 Location** p24 (30–40)

**Author Location** p24

**Epitope** KAFSPEVIPMF

**Epitope name** B57-KF11(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (30–40)

**Author Location**

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p24 (30–40)

**Author Location**

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KAFSPEVIPMF elicited a magnitude of response of 740 SFC with a functional avidity of 0.005nM and binding affinity of 21.

**HXB2 Location** p24 (30–40)  
**Author Location** Gag  
**Epitope** KAFSPEVIPMF  
**Epitope name** KF11  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Country** Australia, Canada, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** rate of progression, immunodominance, optimal epitope  
**References** Streeck *et al.* 2007a

- To characterize HIV-1 proteome areas that are targeted in early, effective CTL responses, two cohorts were studied. Responses in early infection were against fewer epitopes and of lower magnitude than during chronic infection. While no region of the proteome was favored, Nef was the predominant target based on length of proteins. When based on the expression of protective versus nonprotective HLA I alleles, it was found that HLA-B27 and -57 possessing slow progressors to disease directed the majority of their responses to Gag in early infection, as opposed to those with HLA-B\*3501 or B\*3502, i.e. rapid progressors to AIDS, who had negligible responses to Gag. As compared with HLA-B57-/B27-subjects and HLA-B35 subjects, HLA-B57+/27+ subjects responded most to the p24 component of Gag. By using overlapping peptides within Gag p24, two were picked as being consistently targeted, and both contained previously described epitopes TW10 and KK10.
- IVLPEKDSW, i.e. epitope IW9 of RT protein was targeted in 62% of B57+ non-progressors to disease.

**HXB2 Location** p24 (30–40)  
**Author Location**  
**Epitope** KAFSPEVIPMF  
**Epitope name** KF11 ?  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Country** United States, South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding  
**Keywords** memory cells  
**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** p24 (30–40)  
**Author Location**  
**Epitope** KAFSPEVIPMF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Country** Kenya  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining  
**Keywords** responses in children, rate of progression  
**References** Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking attribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Response detected in 1 typically progressing child.

**HXB2 Location** p24 (30–40)  
**Author Location**  
**Epitope** KAFSPEVIPMF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5801, B57)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells  
**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- KAFSPEVIPMF was frequently recognized in children and in adults.

**HXB2 Location** p24 (30–40)  
**Author Location** p24 (153–164)  
**Epitope** KAFSPEVIPMF  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (B57, B58)  
**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance  
**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B57/B58 women, 4/6 HEPS and 12/17 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 2 of the 4/6 HEPS cases and in 7 of the 12/17 HIV-1 infected women.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (30–40)

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B58)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2002

- Neisseria gonorrhoea cervicitis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

**HXB2 Location** p24 (30–40)

**Author Location** p24

**Epitope** KAFSPEVIPMF

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B63)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 60% of B63-positive subjects and 33% of B57/58-positive subjects.

**HXB2 Location** p24 (30–40)

**Author Location** p24 (30–40)

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B58)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (30–40)

**Author Location** p24

**Epitope** KAFSPEVIPMF

**Subtype** B, G

**Immunogen** HIV-1 infection

**Species (MHC)** human (B58)

**Donor MHC** A2, A36, B45, B58, Cw3, Cw6

**Country** Nigeria

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype G Gag. The autologous epitope sequence in this person matched the known epitope.

**HXB2 Location** p24 (30–40)

**Author Location**

**Epitope** KAFSPEVIPMF

**Immunogen**

**Species (MHC)** human (B63)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B63 epitope.

**HXB2 Location** p24 (30–40)

**Author Location** p24

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.

- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized by 1/22 HEPS sex worker controls, ML1250.

**HXB2 Location** p24 (30–40)

**Author Location**

**Epitope** KAFSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, acute/early infection

**References** Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope KAFSPEVIPMF seen in 1 patient, underwent sequence changes.

**HXB2 Location** p24 (31–41)

**Author Location** Gag (171–181)

**Epitope** AFSPEVIPMFT

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p24 (31–44)

**Author Location** p24 (31–44 HXB2)

**Epitope** AFSPEVIPMFALS

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided, it appears to be HXB2.
- Responses to this peptide were detected in 22% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p24 (31–47)

**Author Location** Gag

**Epitope** AFSPEVIPMFSALSEGA

**Epitope name** GAG-23

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187–2200 (2004)].
- This peptide, sqVSQNYPIVQNLQGMV differs from the consensus C sequence kVSQNYPIVQNLQGMV at 2 amino acid positions, i.e. by 11.1%.

**HXB2 Location** p24 (31–47)**Author Location** Gag**Epitope** AFSPEVPMFSALSEGA**Epitope name** GAG-23**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Country** China**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, immunodominance**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, AFSPEVPMFSALSEGA differs from the consensus C sequence AFSPEVPMFtALSEGA at 1 amino acid position, i.e. by 5.9%.

**HXB2 Location** p24 (31–47)**Author Location** p24**Epitope** AFSPEVPMFSALSEGA**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Country** Barbados, Haiti, United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other**Keywords** binding affinity, immunodominance**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3

frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.

- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, AFSPEVPMFSALSEGA, had an overall frequency of recognition of 15.3% - 16.9% AA, 11.5% C, 18.2% H, 9.5% WI. This peptide is included in a 49 aa Gag-p24 highly reactive region to be used for vaccine design. It is also part of 'Region III', PRTLNAWVKVVEEKAFSPEVPMFSALSEGA, a 31 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** p24 (31–50)**Author Location** p24 (163–182)**Epitope** AFSPEVPMFSALSEGATPQ**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** p24 (31–50)**Author Location** p24 (163–182 SF2)**Epitope** AFSPEVPMFSALSEGATPQ**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A2, B21.

**HXB2 Location** p24 (31–50)**Author Location** p24 (163–182 SF2)**Epitope** AFSPEVPMFSALSEGATPQ**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** p24 (31–50)**Author Location** p24 (SF2)**Epitope** AFSPEVPMFSALSEGATPQ**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Altfield *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD4 dependent, but the HLA presenting molecule and optimal epitope were not determined.

**HXB2 Location** p24 (32–40)

**Author Location** Gag (164–172)

**Epitope** FSPEVIPMF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A28, A3, B53, B57

**Assay type** Chromium-release assay

**Keywords** TCR usage, genital and mucosal immunity

**References** Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCR $\beta$  VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood and semen.
- The TCR $\beta$  VDJ rearrangement of a CTL clone from the blood was V $\beta$ 21S3DJ1.2, and a clone from the semen used V $\beta$ 7S1DJ2.3.

**HXB2 Location** p24 (32–40)

**Author Location**

**Epitope** FSPEVIPMF

**Immunogen**

**Species (MHC)** human (B57)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B57 epitope.

**HXB2 Location** p24 (32–40)

**Author Location** p24

**Epitope** FSPEVIPMF

**Epitope name** FF9

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B58, B63)

**Donor MHC** A\*74, A\*8001, B\*18, B\*57, Cw\*02, Cw\*07

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.

- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. Significantly more often recognized by B63+ and B57/58+ subjects than by negative subjects. Optimal epitope defined.

**HXB2 Location** p24 (33–40)

**Author Location** p24 (33–40)

**Epitope** SPEVIPMF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope SPEVIPMF showed >70% conservation across all clades.

**HXB2 Location** p24 (34–49)

**Author Location** p24

**Epitope** PEVIPMFSALSEGATP

**Epitope name** PP16

**Immunogen** in vitro stimulation or selection

**Species (MHC)**

**Assay type** Other

**Keywords** assay standardization/improvement, characterizing CD8+ T cells

**References** Stone *et al.* 2005

- A new microarray technique was developed to screen small samples of T cells for specific peptide-MHC binding and functional responses. Each array element acts as an artificial antigen-presenting cell, consisting of immobilized recombinant MHC-peptide complex, costimulatory molecules, and cytokine-capture antibodies. The elements specifically elicit T-cell responses such as adhesion, secretion of cytokines, and modulation of surface markers.

**HXB2 Location** p24 (35–43)

**Author Location** p24 (167–175 LAI)

**Epitope** EVIPMFSAL

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*2601)

**Keywords** subtype comparisons

**References** Goulder *et al.* 1996a

- Identified as optimal epitope within Gag sequence AFSPEVIPMFSALSEGATPQ.

- Relatively conserved epitope within B clade and in other clades.
- Suspected binding motif for HLA-A26 includes T or V anchor at position 2, negative charge at position 1.
- C. Brander notes that this is an A\*2601 epitope in the 1999 database.

**HXB2 Location** p24 (35–43)  
**Author Location** p24 (167–175 LAI)  
**Epitope** EVIPMFSA  
**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*2601)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes that this is an A\*2601.

**HXB2 Location** p24 (35–43)  
**Author Location** Gag (169–177)  
**Epitope** EVIPMFSA  
**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2601)  
**Country** Japan

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay, Other, HLA binding

**Keywords** subtype comparisons, immunodominance, optimal epitope

**References** Satoh *et al.* 2005

- Reverse immunogenetics was used to identify HIV-1 epitopes presented by HLA-A\*2601. 110 peptides were predicted to bind to HLA-A\*2601. 24 of these were demonstrated to bind through a HLA-A\*2601 stabilization assay. Four of these, including this one, were shown to be epitopes endogenously presented by this allele, that can induce peptide-specific CD8 T-cells. HLA-A\*2601 is common in Asia.
- Immunodominant epitope recognized in 5/7 HIV-infected individuals with HLA-A\*2601. This epitope is highly conserved in clade B and E (CRF01).

**HXB2 Location** p24 (35–43)  
**Author Location** (C consensus)  
**Epitope** EVIPMFAL  
**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2601)  
**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- EVIPMFAL is an optimal epitope.

**HXB2 Location** p24 (35–43)  
**Author Location** Gag (169–177 SF2)  
**Epitope** EVIPMFSA

**Subtype** A, B, C, CRF01\_AE, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2601, A\*2603)

**Country** Japan

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay, HLA binding

**Keywords** binding affinity, subtype comparisons, rate of progression, immunodominance, escape, cross-presentation by different HLA, variant cross-recognition or cross-neutralization

**References** Kawashima *et al.* 2005

- A\*26 is associated with slow progression to disease and is common in Asian populations (about 20%). 31/110 HIV peptides that carried the A\*2603 motif ([VTILP] at P2, [ML] at the C-terminus) bound to HLA-A\*2603. Only 2 of these were epitopes and could induce specific CD8 T-cell responses in PBMC from HLA-A\*2603 positive subjects.
- This epitope induced specific CD8+ T cells in chronically infected individuals with either A\*2603 or A\*2601. It is an immunodominant epitope.
- 3 common B clade variants were synthesized. EVIPMFaAL and EVIPMFtAL bound to A\*2603 with equal affinity as the consensus form, EVIPMFSA, but could not be recognized by an EVIPMFSA-specific T-cell clone so may mediate TCR escape. The other common variant, kVIPMFSA, did not bind to A\*2603.
- EVIPMFSA is the most common form in clades A, B, D, and E (CRF01), but EVIPMFtAL is the most common form in clade C.

**HXB2 Location** p24 (35–43)  
**Author Location** p24 (167–175)  
**Epitope** EVIPMFSA

**Immunogen** HIV-1 infection

**Species (MHC)** human (A26)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for IFN $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope.

**HXB2 Location** p24 (35–43)  
**Author Location** Gag  
**Epitope** EVIPMFSA

**Epitope name** EL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A26)

**Donor MHC** A26, B27

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, rate of progression, immunodominance, escape

**References** Feeney *et al.* 2004



- Viral load in a perinatally infected child remained low until emergence of an escape variant (kTwiiIglNk) in the immunodominant CTL epitope KRWILGLNK when the child was 7.4 years old. The emergence of this escape mutation was followed by an increase in viremia and an increase in the number of targeted CTL epitopes, measured again when the child was 9.2 years old. The EL9 response was not observed until after the escape mutation occurred in the immunodominant epitope, and was detected in the 9.2 year sample for the first time.

**HXB2 Location** p24 (35–43)

**Author Location** p24

**Epitope** EVIPMFSAL

**Epitope name** A26-EL9(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A26)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (35–43)

**Author Location**

**Epitope** EVIPMFSAL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (A26)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p24 (35–49)

**Author Location** p24 (35–48 HXB2)

**Epitope** EVIPMFSALSEGATP

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p24 (36–43)

**Author Location** p24 (168–175 LAI)

**Epitope** VIPMFSAL

**Subtype** B

**Immunogen**

**Species (MHC)** human (Cw\*0102)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a C\*0102(Cw1) epitope.

**HXB2 Location** p24 (36–43)

**Author Location** p24 (36–43 HXB2)

**Epitope** VIPMFSAL

**Epitope name** VL8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0102)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at

high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

**HXB2 Location** p24 (36–43)  
**Author Location** p24 (168–175 LAI)  
**Epitope** VIPMFSAL  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (Cw\*0102, Cw1)  
**References** Goulder *et al.* 1997b

**HXB2 Location** p24 (36–43)  
**Author Location** p24 (168–175)  
**Epitope** VIPMFSAL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw1, Cw2)  
**Keywords** immunodominance  
**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope.

**HXB2 Location** p24 (37–52)  
**Author Location** Gag (169–184 LAI)  
**Epitope** IPMFSALESGATPQDL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B12)  
**References** Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM17 (CDC P2A+C+D2) had a CTL response to two epitopes in Gag.

**HXB2 Location** p24 (37–52)  
**Author Location** p24 (169–184 LAI)  
**Epitope** IPMFSALESGATPQDL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**References** Buseyne *et al.* 1993b

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people.

**HXB2 Location** p24 (37–52)  
**Author Location** p24 (37–52)  
**Epitope** IPMFSALESGATPDQL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (38–48)  
**Author Location** Gag (178–188)  
**Epitope** PMFTALSEGAT  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p24 (38–55)  
**Author Location** Gag  
**Epitope** PMFSALSEGATPQDLNTM  
**Epitope name** GAG-24  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, immunodominance  
**References** Zhao *et al.* 2007

- 46 ART-naïve subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, PMFsALSEGATPQDLNTM differs from the consensus C sequence PMFtALSEGATPQDLNTM at 1 amino acid position, i.e. by 5.6%.

**HXB2 Location** p24 (38–55)  
**Author Location** p24  
**Epitope** PMFSALSEGATPQDLNTM  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004
- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
  - Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
  - In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
  - This immunodominant, frequently targeted overlapping peptide, PMFSALSEGATPQDLNTM, had an overall frequency of recognition of 16% - 20.3% AA, 15.4% C, 13.6% H, 4.8% WI. This peptide is included in a 49 aa Gag-p24 highly reactive region to be used for vaccine design. It is also part of 'Region III', PRTLNAWVKVVEEKAFSPEVPMFSALSEGA, a 31 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** p24 (39–58)

**Author Location** Gag (171–190)

**Epitope** MFTALSEGTPQDLNTMLNT

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** p24 (41–56)

**Author Location** Gag (175–190)

**Epitope** QALSEGCTPYDINQML

**Subtype** HIV-2

**Immunogen** HIV-2 infection

**Species (MHC)** human

**Country** Guinea-Bissau

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** rate of progression, optimal epitope, HIV-2

**References** Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.
- This peptide, QALSEGCTPYDINQML, was recognized by 13 out of 65 subjects. It is found in the 149 amino-acid long HIV-2 proteome region of Gag 175-323.

**HXB2 Location** p24 (41–60)

**Author Location** p24 (41–60 B1 and B2)

**Epitope** SALSEGATPQDLNTMLNTVG

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A03, A32, B08, B62, Cw3)

**Country** Netherlands

**Assay type** Other

**Keywords** subtype comparisons, computational epitope prediction, superinfection

**References** Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01\_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This epitope, SALSEGATPQDLNTMLNTVG, of unknown HLA restriction is strongly reactive in ethnic Africans and deviates to SALSEGATPQDLNmMLNiVG in subtype CRF01\_AE but shows no changes over time. Convergent evolution of this epitope to tALSEGATPQDLNTMLNTVG (S to T) was seen in subtypes B1 and B2 in 92% and 96% viruses after 4 and 3 years respectively. It overlaps with a CD4+ T-cell epitope.

**HXB2 Location** p24 (41–60)

**Author Location** p24 (179–188 subtype A)

**Epitope** SALSEGATPQDLNMLNIVG

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Keywords** subtype comparisons

**References** Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa.
- This CTL epitope is presented by B\*8101 in one of the patients with an A subtype infection – B\*8101 is a newly discovered HLA allele found in Africans, and the epitope has yet to be mapped precisely.
- This epitope is distinct in subtype A relative to subtypes B, C, and D which share the dominant sequence: SALSEGATPQDLNLTMLNTVG.

**HXB2 Location** p24 (41–60)**Author Location** p24 (173–192 SF2)**Epitope** SALSEGATPQDLNLTMLNTVG**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- Three of these 12 had CTL response to this peptide.
- The responding subjects were HLA-A3, A32, B7, B14; and HLA-A2, A3, B14, B44.

**HXB2 Location** p24 (41–60)**Author Location** p24 (173–192 SF2)**Epitope** SALSEGATPQDLNLTMLNTVG**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** p24 (41–60)**Author Location** p24 (SF2)**Epitope** SALSEGATPQDLNLTMLNTVG**Immunogen** HIV-1 infection**Species (MHC)** human**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

**HXB2 Location** p24 (41–62)**Author Location** p24 (173–194 BH10)**Epitope** SALSEGATPQDLNLTMLNTVGGH**Immunogen** HIV-1 infection**Species (MHC)** human (B14)**References** Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

**HXB2 Location** p24 (42–52)**Author Location** Gag (343–353)**Epitope** ALSEGATPQDL**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Country** India**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** subtype comparisons**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p24 (43–52)**Author Location** Gag (175–184 WEAU)**Epitope** LSEGATPQDL**Epitope name** Gag LL10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*4403)**Donor MHC** A\*2902, B\*0801, B\*4403**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** dynamics, immunodominance, escape, kinetics, characterizing CD8+ T cells, viral fitness and reversion**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- There was a weak response to this epitope during acute and early infection, and the epitope sequence did not vary during the first year of the infection.

**HXB2 Location** p24 (43–52)**Author Location** p24 (subtype A)**Epitope** LSEGATPQDL**Subtype** A**Immunogen** HIV-1 infection**Species (MHC)** human (B42, B44)**Keywords** subtype comparisons**References** Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.
- This optimal epitope sequence, recognized by CTL derived from a Ugandan with an A subtype infection (patient SP 511), is cross-reactive with subtypes A, B and D peptides.

**HXB2 Location** p24 (44–52)  
**Author Location** p24 (176–184)  
**Epitope** SEGATPQDL  
**Immunogen**  
**Species (MHC)** human (B\*4001)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*4001, B60 epitope.

**HXB2 Location** p24 (44–52)  
**Author Location** p24  
**Epitope** SEGATPQDL  
**Epitope name** B40-SL9(p24)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B40)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (44–52)  
**Author Location**  
**Epitope** SEGATPQDL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B40)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** supertype, cross-presentation by different HLA  
**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B40), an additional HLA (B44) was statistically predicted to be associated with this epitope.

**HXB2 Location** p24 (44–52)  
**Author Location** Gag (178–186 BRU)  
**Epitope** SEGATPQDL  
**Subtype** B, CRF02\_AG  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Country** Cote D'Ivoire  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons  
**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 1/9 CRF02\_AG-infected Ivoirians, and 1/9 B-infected French subjects.

**HXB2 Location** p24 (44–52)  
**Author Location** p24 (SF2)  
**Epitope** SEGATPQDL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B60)  
**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes.
- B60 is present in 10-20% of the Caucasoid and very common in Asian populations.

**HXB2 Location** p24 (44–52)  
**Author Location** p24  
**Epitope** SEGATPQDL  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B60)  
**Donor MHC** A2, A24, B38, B60, Cw12, Cw2  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** HAART, ART, supervised treatment interruptions (STI), acute/early infection, early treatment  
**References** Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were

fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

**HXB2 Location** p24 (44–52)

**Author Location** p24 (44–52 NL43)

**Epitope** SEGATPQDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Assay type** Chromium-release assay, CTL suppression of replication

**Keywords** escape

**References** Yang *et al.* 2003a

- Virus was cultured in the presence of CTL lines specific for 5 different epitopes (SLYNTVATL, ILKEPVHGV, IEIKDTKEAL, SEGATPQDL, and KEKGGLEGL) to study the emergence of escape mutations. Escape varied between clones for the same epitope, and between different epitopes. Gag and RT epitope escape, if it occurred at all, tended to be monoclonal and within the epitope, indicating strong fitness constraints, while the Nef epitope escape was rapid, polyclonal, and sometimes the result of upstream frameshifts.
- One CTL clone, 161Jx12, recognized this epitope, and apparently no resistance mutations were selected by this clone, although the data was not shown in the paper.

**HXB2 Location** p24 (44–52)

**Author Location** p24 (176–184)

**Epitope** SEGATPQDL

**Epitope name** Gag/p24-SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Assay type** Chromium-release assay

**Keywords** binding affinity, TCR usage, characterizing CD8+ T cells

**References** Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 1/14 CTL T-cell clones tested were specific for Gag/p24-SL9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 value for Gag/p24-SL9 was 30 pg/ml, it was among the peptides with the highest avidity.

**HXB2 Location** p24 (44–52)

**Author Location** p24 (HXB2)

**Epitope** SEGATPQDL

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (B60)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** epitope processing, vaccine antigen design, characterizing CD8+ T cells

**References** SenGupta *et al.* 2004

- Multiple HLA class I-restricted and class II-restricted T-cell epitopes were shown to be processed and presented from an exogenously added HIV-1 gag-p24 peptide complexed to a heat shock protein. T-cell recognition of the complex was shown to be inhibited by brefeldin A indicating an endoplasmic reticulum-dependent pathway.

**HXB2 Location** p24 (44–52)

**Author Location** p24 (44–52)

**Epitope** SEGATPQDL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60, B61)

**Keywords** immunodominance

**References** Day *et al.* 2001

- No immunodominant responses were detected to five B61-restricted epitopes tested.
- All five B60-restricted epitopes were reactive in another subject, the strongest CTL response directed against the B60-epitope p24 SEGATPQDL, and the B60-restricted responses together contributed over one-third of the total CTL response.

**HXB2 Location** p24 (45–59)

**Author Location** Gag (178–192)

**Epitope** EGATPQDLNTMLNTV

**Epitope name** EV15

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- One subject responded to peptide EV15, a non-B\*57-restricted peptide.

**HXB2 Location** p24 (46–59)

**Author Location** p24 (SF2)

**Epitope** GATPQDLNTMLNTV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ African American living in Boston with HLA A\*3002/68 B14/\*5802 Cw6/8 – this epitope fell within the most recognized peptides in the study.

- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNMLNTVGG (p24 41-60), and WEKIRLRPGGKKKYK (p17 16-30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNMLNTVGG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (46–62)

**Author Location** p24

**Epitope** GATPQDLNMLNTVGGH

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J.Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, GATPQDLNMLNTVGGH, had an overall frequency of recognition of 20% - 18.6% AA, 11.5% C, 18.2% H, 4.8% WI. This peptide is included in a 49 aa Gag-p24 highly reactive region to be used for vaccine design. It is also part of 'Region III', PRTLNAWVKVVEEKAFSPEVIMFMSALSEGA, a 31 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** p24 (47–55)

**Author Location** p24 (47–55)

**Epitope** ATPQDLNTM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (47–56)

**Author Location** p24 (subtype A)

**Epitope** ATPQDLNMLM

**Subtype** A

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B53)

**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T-cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** p24 (47–58)

**Author Location** Gag (181–192)

**Epitope** CTPYDINQMLNC

**Subtype** HIV-2

**Immunogen** HIV-2 infection

**Species (MHC)** human (B58)

**Country** Gambia

**Keywords** HIV-2

**References** Bertoletti 1998

- HIV-2 epitope defined from an infection in Gambia, Bertoletti, pers. comm.

**HXB2 Location** p24 (47–58)

**Author Location** p24

**Epitope** ATPQDLNMLNT

**Subtype** B, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B58)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell

responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.

- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence in this person matched the known epitope.

**HXB2 Location** p24 (48–55)

**Author Location** p24 (48–55)

**Epitope** TPQDLNTM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

**HXB2 Location** p24 (48–56)

**Author Location** Gag (180–188)

**Epitope** TPQDLNTML

**Subtype** A, C, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07, B\*42, B\*81)

**Country** Tanzania

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, immunodominance

**References** Geldmacher *et al.* 2007a

- To assess whether T-cell specific responses to Gag and Nef are biased towards infecting subtype recombination, 56 ART-naive subjects were studied using six overlapping peptide sets consisting 15-mer peptides, covering both proteins completely. A multi-region hybridization assay was employed. Overall, the best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants TPQDLNtML and TPQDLNmML were studied as peptide sequences EGA-TPQDLNtML-NTV (subtypes C and D) and EGA-TPQDLNmML-NIV (subtype A), with 41% responders. Subtypes C and D epitopes were best recognized.

**HXB2 Location** p24 (48–56)

**Author Location** p24 (180–188 IIIB)

**Epitope** TPQDLNTML

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0702 epitope.

**HXB2 Location** p24 (48–56)

**Author Location** p24

**Epitope** TPQDLNTML

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B\*0702)

**Assay type** Tetramer binding

**Keywords** binding affinity

**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, TPQDLNTML (MHC Class I restriction, serotype Bw6) complexed with MHC B\*0702 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

**HXB2 Location** p24 (48–56)

**Author Location** (C consensus)

**Epitope** TPQDLNTML

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3910)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the L9 residue of TPQDLNTML are associated with the presence of the HLA presenting molecule in the host.
- TPQDLNTML is cross-presented by B\*8101 and B\*3901.

**HXB2 Location** p24 (48–56)

**Author Location**

**Epitope** TPQDLNTML

**Immunogen**

**Species (MHC)** human (B\*3910)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B\*3910 epitope.

**HXB2 Location** p24 (48–56)

**Author Location** p24 (48–56)

**Epitope** TPQDLNTML

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B\*3910)

**Country** South Africa



- Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** optimal epitope  
**References** Honeyborne *et al.* 2006
- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B\*3910, B\*4201, B\*8101 and Cw\*1801, by motif inference. HLA-A\*2902 was found to overlap those of A1 and A24 supertypes.
  - TPQDLNTML was the optimal epitope for HLA-B\*3910 with variants TPQDLNTM, PQDLNTML, TPQDLNTMLn, aTPQDLNTML having been tested.
- HXB2 Location** p24 (48–56)  
**Author Location** p24 (179–187 LAI)  
**Epitope** TPQDLNTML  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (B\*4201)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is a B\*4201 epitope.
- HXB2 Location** p24 (48–56)  
**Author Location** (C consensus)  
**Epitope** TPQDLNTML  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - TPQDLNTML is an optimal epitope.
- HXB2 Location** p24 (48–56)  
**Author Location** p24  
**Epitope** TPQDLNTML  
**Epitope name** TL9  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization  
**Keywords** rate of progression  
**References** Day *et al.* 2007
- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
  - The tetramer B\*4201 TL9 was used to test 38 patients and gave a median ex vivo tetramer frequency of 2.23.

- HXB2 Location** p24 (48–56)  
**Author Location** p24  
**Epitope** TPQDLNTML  
**Epitope name** TL9  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization  
**Keywords** rate of progression  
**References** Day *et al.* 2007
- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
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- HXB2 Location** p24 (48–56)  
**Author Location**  
**Epitope** TPQDLNTML  
**Epitope name** TL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** proliferation, Tetramer binding, Intracellular cytokine staining  
**References** Day *et al.* 2006
- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.
- HXB2 Location** p24 (48–56)  
**Author Location** Gag (96ZM651.8)  
**Epitope** TPQDLNTML  
**Epitope name** G180-TL9  
**Immunogen**  
**Species (MHC)** human (B\*4201, B\*8101)  
**Keywords** subtype comparisons, immunodominance  
**References** Novitsky *et al.* 2001
- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
  - 19/46 (41.3%) had CTL responses to one or more peptides within the first immunodominant region of Gag (peptides TLNAWVKVIEEKAFSPEVIP, EKAFSPEVIPMFTALSEGAT, and MFTALSEGATPQDLNTMLNT), with magnitudes of response with ELISPOT results median and range 495 (103 to 1,447) SFC/10<sup>6</sup> PBMC
  - 7/11 HLA-A\*4201+ subjects (64%) responded to peptide MFTALSEGATPQDLNTMLNT.
  - TPQDLNTML is a A\*4201 epitope within TLNAWVKVIEEKAFSPEVIP.

**HXB2 Location** p24 (48–56)  
**Author Location** p24  
**Epitope** TPQDLNTML  
**Epitope name** TL-9  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201, B\*8101)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay  
**Keywords** subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA

**References** Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles.
- TPQDLNTML was presented by B\*4201 and B\*8101. B\*44 is more common among Caucasians than Zulus (allele frequency 0.149 versus 0.107), while A\*29 is more common in Zulus (0.045 versus 0.125). This epitope had previously identified in B clade infections.

**HXB2 Location** p24 (48–56)  
**Author Location** Gag (180–188)  
**Epitope** TPQDLNTML  
**Epitope name** TL9  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201, B\*8101)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other  
**Keywords** supertype, escape, cross-presentation by different HLA, TCR usage, HLA associated polymorphism  
**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity was correlated with selection pressure observed in HLA allele-epitope restriction.
- TL9 selection pressure was evidenced by studying changing epitope variants associated with HLAs of the B7 supertype.
- Higher level of polymorphism variation, escape mutations and TCR diversity was associated with the B\*8101 allele.

- In 3 B-supertype alleles studied, B\*4201, B\*8101 and B\*3910, the variant at the seventh position, TPQDLN $\gamma$ ML, was most common. Several more variants are listed in the paper.

**HXB2 Location** p24 (48–56)  
**Author Location** Gag  
**Epitope** TPQDLNTML  
**Epitope name** TL9  
**Subtype** A, C, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702, B\*4201, B\*8101)  
**Country** Tanzania  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** rate of progression, immunodominance  
**References** Geldmacher *et al.* 2007b

- The objectives of this study were to find antiviral epitopic determinants of Gag HIV-specific CTL response and to find 'host HLA-CTL response' correlations. By studying 56 ART-naive subjects including low viral load (LVL) responders, the authors show that subjects expressing the above "protective" HLA have broader Gag epitope recognition which may be abrogated if co-expressed with HLA-B alleles associated with rapid AIDS progression. Also, a negative linear relation was seen between Gag epitope numbers recognized and plasma viral load while a positive relationship was seen with CD4 T-cell count. Finally, LVL subjects recognized specific Gag regions at the N- and C-termini of the protein more often than peptides in the middle of the protein.
- Epitope TPQDLNTML elicits a strong CTL-response and was targeted with high magnitude by 41% of the subjects. TL9 is highly conserved in subtype C and shows no evidence of viral escape by point mutations. The authors however, find no evidence of this immunodominant response having a substantial role, as subjects with B\*8101 who do target TL9 have high viral loads.

**HXB2 Location** p24 (48–56)  
**Author Location** Gag  
**Epitope** TPQDLNMML  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4202)  
**Country** Kenya  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization  
**References** Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRF-FKTL (YL9 from Gag protein) was observed and restricted to Cw0304.

- The sequences egaTPQDLNMMLniv and egaTPQDLNtML-ntv are associated with HLA-B\*4202 and contain the epitope TPQDLNMML (TL9). Subtype specificity was seen as the variant epitope TPQDLNtML was rarely cross-reacted with.

**HXB2 Location** p24 (48–56)

**Author Location** Gag (173–181 HIV-2)

**Epitope** TPYDINQML

**Subtype** HIV-2

**Immunogen** HIV-2 infection

**Species (MHC)** human (B\*5301)

**Keywords** optimal epitope, HIV-2

**References** Frahm *et al.* 2008

- C. Brander notes this is a HIV-2 B\*5301 epitope.

**HXB2 Location** p24 (48–56)

**Author Location** p24

**Epitope** TPQDLNMML

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B\*53C1)

**Assay type** Tetramer binding

**Keywords** binding affinity

**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, TPQDLNMML (MHC Class I restriction, serotype Bw4Ile80) complexed with MHC B\*53C1 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

**HXB2 Location** p24 (48–56)

**Author Location** (48–56)

**Epitope** TPQDLNTML

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*81)

**Assay type** Other

**Keywords** epitope processing, HLA associated polymorphism

**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.

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- TPQDLNTML was a previously defined B\*81 presented epitope that encompassed associated polymorphisms, SeGAI/TPQDLNtML, in the seventh position of as well in the third position before the known epitope.

**HXB2 Location** p24 (48–56)

**Author Location** p24 (180–188 LAI)

**Epitope** TPQDLNTML

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*8101 epitope.

**HXB2 Location** p24 (48–56)

**Author Location** (C consensus)

**Epitope** TPQDLNTML

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the T7 residue of TPQDLNTML are associated with the presence of the HLA presenting molecule in the host.
- TPQDLNTML is cross-presented by B\*8101 and B\*3901.

**HXB2 Location** p24 (48–56)

**Author Location** p24

**Epitope** TPQDLNTML

**Epitope name** TL9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization

**Keywords** rate of progression

**References** Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B\*8101 TL9 was used to test 15 patients and gave a median ex vivo tetramer frequency of 1.00.

**HXB2 Location** p24 (48–56)**Author Location** p24**Epitope** TPQDLNTML**Epitope name** TL9**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*8101)**Country** South Africa**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization**Keywords** rate of progression**References** Day *et al.* 2007

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- The tetramer B\*8101 TL9 was used to test 15 patients and gave a median ex vivo tetramer frequency of 1.00.

**HXB2 Location** p24 (48–56)**Author Location** Gag**Epitope** TPQDLNTML**Epitope name** TL9**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*8101)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** rate of progression, HLA associated polymorphism**References** Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than "other" HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by "other", non-advantageous HLA I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also showed lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.

- Variants TPDLNTML and TPQDLNsML at positions 3 and 7 were the predominant polymorphisms found.

**HXB2 Location** p24 (48–56)**Author Location****Epitope** TPQDLNTML**Epitope name** TL9**Immunogen** HIV-1 infection**Species (MHC)** human (B\*8101)**Country** South Africa**Assay type** proliferation, Tetramer binding, Intracellular cytokine staining**References** Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

**HXB2 Location** p24 (48–56)**Author Location****Epitope** TPQDLNTML**Epitope name** Gag-TL9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5301, B\*8101, B7)**Donor MHC** A\*3402, A\*7401, B\*5301, B\*8101, Cw\*0401, Cw\*0802**Keywords** HAART, ART**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subjects 00RCH86 and 03RCH59 both recognized this epitope, both restricted by HLA B\*8101.
- Subject 00RCH86 was African American, not on HAART, viral load 51000, CD4 count 520.
- Subject 03RCH59 was African American, male, on HAART, viral load 22000, CD4 count 769.
- Among HIV+ individuals who carried HLA B07, 2/9 (22%) recognized this epitope.
- Among HIV+ individuals who carried HLA B\*5301, 3/15 (20%) recognized this epitope.
- Among HIV+ individuals who carried HLA B81, 4/6 (67%) recognized this epitope.

**HXB2 Location** p24 (48–56)**Author Location****Epitope** TPQDLNTML**Immunogen** HIV-1 infection**Species (MHC)** human (B07)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** binding affinity, immunodominance, optimal epitope**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope TPQDLNTML elicited a magnitude of response of 659 SFC with a functional avidity of 0.75nM and binding affinity of 4597nM.

**HXB2 Location** p24 (48–56)

**Author Location**

**Epitope** TPQDLNTML

**Immunogen** HIV-1 infection

**Species (MHC)** human (B07, B42, B53, B81)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 4 alleles previously known to be associated (B07, B42, B53, B81) and 3 additional alleles (A02, A24, B14).

**HXB2 Location** p24 (48–56)

**Author Location** (C consensus)

**Epitope** TPQDLNTML

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201, B\*8101, B39, Cw\*0802)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (48–56)

**Author Location** p24 (C consensus)

**Epitope** TPQDLNTML

**Immunogen** HIV-1 infection

**Species (MHC)** human (B42)

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- B42 and B81 are very similar, and both can present this epitope to B42-positive effector cells – this epitope is almost certainly optimal for B81 as well – B42 and or B81 are expressed in 40–45% of Zulu and Xhosa infected individuals in South Africa, and in 14/18 B42 or B81+ individuals, the dominant gag response was to TPQDLNTML.
- Three peptides GSEELRSLYNTVATL (p17 residues 71–85), SALSEGATPQDLNTMLNTVG (p24 41–60), and WEKIRLRPGGKKKYKCLK (p17 16–30) contained the dominant Gag-specific epitope in 31/44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20–36), ELRSLYNTVATLYCV (p17Gag 74–88), SALSEGATPQDLNTMLNTVG (p24 41–60), FRDYVDRFFKTLRAEQA (p24 161–177), and SILDIKQGKEPFRDY (p24 149–164) contained dominant Gag-specific epitopes in 32/37 C-clade infected subjects.

**HXB2 Location** p24 (48–56)

**Author Location** Gag

**Epitope** TPQDLNTML

**Immunogen** HIV-1 infection

**Species (MHC)** human (B42)

**References** Goulder *et al.* 2000b

- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA]).
- HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection.

**HXB2 Location** p24 (48–56)

**Author Location**

**Epitope** TPQDLNTML

**Epitope name** TL9 ?

**Immunogen** HIV-1 infection

**Species (MHC)** human (B42)

**Country** United States, South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** memory cells

**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T

cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** p24 (48–56)

**Author Location** p24

**Epitope** TPQDLNQML

**Immunogen**

**Species (MHC)** human (B53)

**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: TPYDINQML, no cross-reactivity, Gotch *et al.* [1993]

**HXB2 Location** p24 (48–56)

**Author Location** Gag (173–181)

**Epitope** TPYDINQML

**Subtype** HIV-2

**Immunogen** HIV-2 infection

**Species (MHC)** human (B53)

**Country** Gambia

**Keywords** HIV-2

**References** Gotch *et al.* 1993

- HIV-2 Gag-specific responses were studied in 9 Gambian HIV-2 patients. High levels of HIV-2 Gag-specific CTL were found in all B53+ patients.
- Two HIV-2-positive B53+ patients reacted to this epitope, but failed to react to the HIV-1 equivalent peptide. One HIV-1-positive B53+ patient failed to react to this HIV-2 epitope. Thus, this epitope is unlikely to provide HIV1/HIV2 cross-protection.

**HXB2 Location** p24 (48–56)

**Author Location** Gag (180–188 subtype A)

**Epitope** TPQDLNMML

**Subtype** A

**Immunogen** HIV-1 infection, in vitro stimulation or selection

**Species (MHC)** human (B53)

**Keywords** subtype comparisons

**References** Dorrell *et al.* 2001

- In vitro restimulation of CTL specific for dominant epitopes from infected individuals is possible using recombinant modified vaccinia virus Ankara (MVA) carrying A or D subtype HIV-1 Gag proteins.

**HXB2 Location** p24 (48–56)

**Author Location** p24 (180–188 subtype A consensus)

**Epitope** TPQDLNMML

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Keywords** subtype comparisons, immunodominance, TCR usage

**References** Dorrell *et al.* 2001

- In clade A infected Gambians, three HLA-B53 epitopes were defined in Gag p24 using ELISPOT, tetramer, and cytotoxicity assays.
- This optimal epitope was identified within the 20 mer reactive peptide that carried it by homology with a B53 epitope from HIV-2, a B subtype B7 peptide that corresponds to it, as B53 is part of the B7 superfamily, and by the proline in the anchor at position 2.
- TPQDLNMML was recognized in 6/7 HLA-B53 subjects and was immunodominant in most subjects.
- TPQDLNMML was A subtype-specific with no cross-recognition of the subtype B, C, and D variant, TPQDLNTML, although the B/C/D variant bound more efficiently to B53 – position 7 show great positional variation in crystal structures of two HLA-B53 complexes, suggesting variation here might significantly alter the position of the peptide in the binding groove and thus affect TCR interactions.
- Only one subject might have had a cross-reactive response with the HIV-2 and Mamu-A\*01 variant CTPYDINQML, and this subject might have been dual infected with HIV-2.

**HXB2 Location** p24 (48–56)

**Author Location** p24

**Epitope** TPQDLNMML

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Assay type** Intracellular cytokine staining

**Keywords** immunodominance, genital and mucosal immunity

**References** Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T cells responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 2/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

**HXB2 Location** p24 (48–56)

**Author Location** Gag (180–188)

**Epitope** TPQDLNMML

**Epitope name** TPQ

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Country** Gambia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Flow cytometric T-cell cytokine assay

**Keywords** characterizing CD8+ T cells, HIV-2

**References** Gillespie *et al.* 2005

- CD8 T-cell responses were evaluated and compared in HIV-1 and HIV-2 infected individuals living in the Gambia. A significantly greater magnitude and breadth of Gag-specific responses were found in HIV-1 infected individuals, possibly because of low or undetectable viral loads in HIV-2 infected

individuals. This finding suggests that responses in HIV-2 infection reflect antigen load in plasma, as is the case in HIV-1 infection. No correlation was found between immune control of HIV-2 and the frequency of perforin-expressing virus-specific CD8 T-cells.

- 5/7 HIV-1-infected B53-positive subjects recognized TPQDL-NMML, the HIV-1 version of this epitope. 3/3 HIV-2-infected B53-positive subjects responded to TPYDINQML, the HIV-2 version of the epitope.

**HXB2 Location** p24 (48–56)

**Author Location** Gag (180–188)

**Epitope** TPYDINQML

**Epitope name** TPY

**Subtype** HIV-2

**Immunogen** HIV-2 infection

**Species (MHC)** human (B53)

**Country** Gambia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Flow cytometric T-cell cytokine assay

**Keywords** characterizing CD8+ T cells, HIV-2

**References** Gillespie *et al.* 2005

- CD8 T-cell responses were evaluated and compared in HIV-1 and HIV-2 infected individuals living in the Gambia. A significantly greater magnitude and breadth of Gag-specific responses were found in HIV-1 infected individuals, possibly because of low or undetectable viral loads in HIV-2 infected individuals. This finding suggests that responses in HIV-2 infection reflect antigen load in plasma, as is the case in HIV-1 infection. No correlation was found between immune control of HIV-2 and the frequency of perforin-expressing virus-specific CD8 T-cells.
- 5/7 HIV-1-infected B53-positive subjects recognized TPQDL-NMML, the HIV-1 version of this epitope. 3/3 HIV-2-infected B53-positive subjects responded to TPYDINQML, the HIV-2 version of the epitope.

**HXB2 Location** p24 (48–56)

**Author Location** p24 (180–188 IIIB)

**Epitope** TPQDLNTML

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- No variants of this epitope were found in a non-transmitting mother that had a CTL response to this epitope.

**HXB2 Location** p24 (48–56)

**Author Location** p24 (180–188)

**Epitope** TPQDLNTML

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** immunodominance

**References** Jin *et al.* 2000b

- This is the optimal epitope for the immunodominant response defined using a conventional approach in an HLA B7+ long-term non-progressor.
- Three additional sub-dominant HLA B7 epitopes were defined using EpiMatrix, a non-anchor based strategy for defining potential epitopes, which highlighted 2078 possible epitopes in the autologous HIV-1 derived from the study subject – this was followed by B7 anchor residue prediction which narrowed the set to 55 peptides, three of which could serve as functional CTL epitopes.

**HXB2 Location** p24 (48–56)

**Author Location** p24 (SF2)

**Epitope** TPQDLNTML

**Epitope name** TL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Goulder *et al.* 2001a

- Recognized by patient 9354 during chronic infection, used as a positive control in a study of the SLYNTVATL epitope.

**HXB2 Location** p24 (48–56)

**Author Location** p24 (48–56)

**Epitope** TPQDLNTML

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2–8 out of 11 B7-restricted epitopes.
- An acute seroconverter homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

**HXB2 Location** p24 (48–56)

**Author Location** p24 (48–56)

**Epitope** TPQDLNTML

**Epitope name** B7-TL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.

- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 1/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** p24 (48–56)

**Author Location** p24

**Epitope** TPQDLNTML

**Epitope name** B7-TL9(p24)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A32, B14, B7

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Altfield *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8+ T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient A displayed the greatest response to epitope B14-EL9(gp41), a strong response to B7-TL9(p24), and responses to B7-TM9(Nef) and A32-PW10(RT).

**HXB2 Location** p24 (48–56)

**Author Location** p24 (48–56)

**Epitope** TPQDLNTML

**Epitope name** B7-TL9 Gag

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfield *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response, but in this case the epitope did not vary.

**HXB2 Location** p24 (48–56)

**Author Location** (B consensus)

**Epitope** TPQDLNTML

**Epitope name** TL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A03, B07, Cw7

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope

**HXB2 Location** p24 (48–56)

**Author Location** p24 (HXB2)

**Epitope** TPQDLNTML

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (B42, B7, Cw8)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** epitope processing, vaccine antigen design, characterizing CD8+ T cells

**References** SenGupta *et al.* 2004

- Multiple HLA class I-restricted and class II-restricted T-cell epitopes were shown to be processed and presented from an exogenously added HIV-1 gag-p24 peptide complexed to a heat shock protein. T-cell recognition of the complex was shown to be inhibited by brefeldin A indicating an endoplasmic reticulum-dependent pathway.

**HXB2 Location** p24 (48–56)

**Author Location**

**Epitope** TPQDLNTML?

**Epitope name** TL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B81)

**Country** United States, South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** memory cells

**References** Wherry *et al.* 2006



- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** p24 (48–56)  
**Author Location** p24 (180–188 LAI)  
**Epitope** TPQDLNTML  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*0802)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a C\*0802(Cw8) epitope.

**HXB2 Location** p24 (48–56)  
**Author Location** (C consensus)  
**Epitope** TPQDLNTML  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*0802)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- TPQDLNTML is an optimal epitope.

**HXB2 Location** p24 (48–56)  
**Author Location** Gag (180–188)  
**Epitope** TPQDLNTML  
**Epitope name** TL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw8)  
**Donor MHC** A\*02, A\*68, B\*14, B\*52, Cw\*08, Cw\*12  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** escape, optimal epitope  
**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.

- The B consensus form of this epitope, TPQDLNTML, persisted throughout 6 years of chronic infection in 1 individual.

**HXB2 Location** p24 (48–56)  
**Author Location** p24  
**Epitope** TPQDLNTML  
**Epitope name** Cw8-TL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw8)  
**Donor MHC** A2, A68, B14, B44, Cw5, Cw8  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, escape, acute/early infection, antibody generation, co-receptor, immune evasion  
**References** Streeck *et al.* 2007b

- A subject with acute and rapid disease progression to AIDS showed no neutralizing antibody activity and rapid decline in HIV-specific CTL response by 6 months post-infection. Virus from this rapid progressor was resistant to neutralization by plasma from a long-term progressor. Viral epitopes did not vary much. This suggests viral immune evasion in the absence of viral sequence variation.
- This epitope, TPQDLNTML, elicited a sub-dominant CTL response, not detectable after 6 months post-infection. TL9 and its flanking sequences EGATPQDLNTMLNTV did not show any escape mutations.

**HXB2 Location** p24 (48–56)  
**Author Location** Gag  
**Epitope** TPQDLNTML  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** assay standardization/improvement, epitope processing, characterizing CD8+ T cells  
**References** Beattie *et al.* 2004

- This study compared CD8+ T-cell EliSpot responses to 58 Gag peptides that were optimal epitopes, with responses to overlapping 15 mers that spanned Gag. When screening for HIV-1-specific CD8+ T-cell responses from 49 HIV+ people, overlapping 15-mer peptide pools revealed several novel responses that would have been missed using predefined CD8 epitopes. However, the 15-mer pools often missed low-level responses to predefined epitopes, especially when the epitope was located centrally in the 15-mer peptide, and the overall level of response to the 15 mers was generally lower (mean 1.4 five fold dilutions lower, range 0-3).
- The response to TPQDLNTML was used as an example of a titration curve. When comparing the peptide TPQDLNTML to the 15 mer EGATPQDLNTMLNTV, the 15 mer had a diminished response to the same amount of peptide.

**HXB2 Location** p24 (48–57)  
**Author Location** Gag  
**Epitope** TPQDLNMLN  
**Immunogen**  
**Species (MHC)** human (B7)

**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFN $\gamma$  production in an ELISPOT assay.
- TPQDLNMMLN was newly defined as an HLA-B7 epitope in this study, although it was previously published as a B\*8101 epitope.
- TPQDLNMMLN was shown to stimulate an ELISPOT response, but could not be shown to bind to HLA-B7.
- The variant TPQDLNTMLN was cross-reactive, had previously been identified as a HLA-B14 epitope, and could bind to HLA-B7.

**HXB2 Location** p24 (48–57)**Author Location** Gag**Epitope** TPQDLNMMLN**Epitope name** 1309**Subtype** multiple**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Donor MHC** A03, A24, B07, B38, Cw07, Cw12/13**Country** United States**Assay type** T-cell Elispot**Keywords** binding affinity, computational epitope prediction**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for TPQDLNMMLN: 31%.

**HXB2 Location** p24 (48–57)**Author Location** Gag**Epitope** TPQDLNTMLN**Epitope name** 1308**Subtype** multiple**Immunogen** HIV-1 infection**Species (MHC)** human (B14, B7)**Country** United States**Assay type** T-cell Elispot**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.

- Estimated binding probability for TPQDLNTMLN: 31%. This epitope was not confirmed in this study, but has been reported to be a B14 epitope.

**HXB2 Location** p24 (48–59)**Author Location** p24**Epitope** TPQDLNQMLNTV**Subtype** B, G**Immunogen** HIV-1 infection**Species (MHC)** human (B58)**Donor MHC** A2, A36, B45, B58, Cw3, Cw6**Country** Nigeria**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, variant cross-recognition or cross-neutralization**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype G Gag. The autologous epitope sequence in this person differed from the known epitope in one position, Q7T, TPQDLNtMLNTV

**HXB2 Location** p24 (48–62)**Author Location** p24 (48–56)**Epitope** TPQDLNMMLNIVGGH**Subtype** A, D**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A\*0201, A\*2902, B\*1402, B\*1503; A\*0101, A\*7401, B\*5801**Country** Uganda**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, variant cross-recognition or cross-neutralization**References** Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- This sequence contains a known B7 and B53 epitope, but the subjects recognizing it are B7- and B53-negative. It was conserved in the two people that recognized the peptide.

**HXB2 Location** p24 (49–57)**Author Location** p24 (181–189 LAI)

**Epitope** PQDLNTMLN

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14, Cw8)

**References** Lubaki *et al.* 1997

- Eighty two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response.
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response.
- Despite this being a well defined conserved epitope, none of the 11 gag-specific clones from a B-14 positive subject could recognize either it or p24 RAEQASQEV.
- Christian Brander notes that B14 and Cw8 are in linkage disequilibrium, and that this epitope may be Cw8.

**HXB2 Location** p24 (51–59)

**Author Location** p24 (subtype A)

**Epitope** DLNMLNIV

**Subtype** A

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B14)

**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T-cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T-cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T-cell epitopes: DTVLEDINL (3 individuals), SLYNT-VATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** p24 (51–59)

**Author Location** p24

**Epitope** DLNMLNIV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML1792.

**HXB2 Location** p24 (51–59)

**Author Location** p24 (183–191 LAI)

**Epitope** DLNTMLNTV

**Epitope name** G5

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** HAART, ART

**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** p24 (51–59)

**Author Location** p24 (183–191)

**Epitope** DLNMLNIV

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B14)

**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- Variants DLNMLNIV/DLNTMLNVV are specific for clades A/B.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B14 women, 4/4 HEPS and 3/7 HIV-1 infected women recognized this epitope, likelihood ratio 4.8, p value 0.1, and HEPS women tended to respond to DLNMLNIV/DLNTMLNVV, while infected women tended to respond to DRF(F/W)KTLRA.
- The dominant response to this HLA allele was to this epitope for all 4/4 HEPS cases and in only one of the 3/7 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A\*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Four epitopes were considered to be “resistant epitopes”, as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILK(D/E)PVHGV in RT, A\*6802 DTVLEDINL in Protease, B14 DLN(M/T)LN(I/V)V in p24 and B18 FRDYV-DRF(Y/F)K also in p24.

**HXB2 Location** p24 (51–59)  
**Author Location** p24  
**Epitope** DLNMLNIV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2002

- Neisseria gonorrhoea cervicitis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhoea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

**HXB2 Location** p24 (51–59)  
**Author Location** p24 (183–191 LAI)  
**Epitope** DLNMLNIV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14, Cw8)  
**References** Johnson *et al.* 1992; Nixon *et al.* 1988

- Recent evidence indicates this is a Cw8 epitope; B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication).

**HXB2 Location** p24 (51–59)  
**Author Location** p24  
**Epitope** DLNMLNIV  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (B14, Cw8)  
**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)  
**References** Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is identical to the B clade epitope.
- The D subtype consensus is dLNmMLNiV.
- Recent evidence indicates this is a Cw8 epitope; B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication).

**HXB2 Location** p24 (51–59)  
**Author Location** p24 (183–191 LAI)  
**Epitope** DLNMLNIV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw8)  
**Keywords** review  
**References** McMichael & Walker 1994

- Review of HIV CTL epitopes – defined by B14 motif found within a larger peptide.
- Recent evidence indicates this is a Cw8 epitope; B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication).

**HXB2 Location** p24 (51–59)  
**Author Location** p24 (subtype B)  
**Epitope** DLNMLNIV  
**Subtype** B  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (B\*1402, Cw8)  
**Keywords** subtype comparisons  
**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope, DLNMLNIV, was preferentially recognized by CTL.
- Recent evidence indicates this is a Cw8 epitope; B14 and Cw8 are in linkage disequilibrium and the HLA presenting molecule is hard to distinguish (P. Goulder, personal communication).

**HXB2 Location** p24 (51–59)  
**Author Location** p24  
**Epitope** DLNMLNIV  
**Immunogen** HIV-1 infection  
**Species (MHC)** chimpanzee  
**References** Santra *et al.* 1999

- 3/4 animals displayed HIV-1 Gag-specific CTL activity.
- Effector cells from two chimpanzees were able to recognize two epitopes also recognized by human HIV-1 Gag-specific CTL (SPRTLNAWV, HLA-B7, and DLNMLNIV, HLA-B14).
- No chimpanzee CTL were detected to the following human HIV-1 specific Gag epitopes, although they were embedded within 20mer peptides that contained a reactive epitope: ISPRTLNAW, HLA-B57; KRWILGLNK, HLA-B27; and DRFYKTLRA, HLA-B14.

**HXB2 Location** p24 (51–60)  
**Author Location** Gag  
**Epitope** DLNMLNIVG  
**Epitope name** 1238  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2, B14)  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA  
**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for DLNTMLNTVG: 65%. This epitope was not confirmed in this study, but was previously reported to be presented by B14.

**HXB2 Location** p24 (51–70)  
**Author Location** p24 (183–202 SF2)  
**Epitope** DLNTMLNTVGGHQAAMQMLK

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A26, A30, B38.

**HXB2 Location** p24 (51–82)  
**Author Location** Gag (183–214 LAI)  
**Epitope** DLNTMLNTVGGHQAAMQMLKETINEEAAEWDR  
**Subtype** B

**Immunogen** vaccine  
*Vector/Type:* lipopeptide  
**Species (MHC)** human  
**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 2/10 reacted to this peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual.
- None of the 12 tested had an IgG response to this peptide.

**HXB2 Location** p24 (53–66)  
**Author Location** Gag (188–201)  
**Epitope** NTMLNTVGGHQAAM  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.

- 1/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p24 (60–70)  
**Author Location** Gag (195–205)  
**Epitope** GGHQAAMQMLK  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p24 (61–69)  
**Author Location** p24 (61–69)  
**Epitope** GHQAAMQML

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1510)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** p24 (61–69)  
**Author Location** (C consensus)  
**Epitope** GHQAAMQML  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1510)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (61–69)  
**Author Location** (C consensus)  
**Epitope** GHQAAMQML  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1510)  
**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- GHQAAMQML is an optimal epitope.

**HXB2 Location** p24 (61–69)  
**Author Location** p24 (193–201 LAI)  
**Epitope** GHQAAMQML  
**Subtype** B

**Immunogen**  
**Species (MHC)** human (B\*3901)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*3901 epitope.

**HXB2 Location** p24 (61–69)  
**Author Location** Gag (193–201 IIIB)  
**Epitope** GHQAAMQML  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B38)  
**Assay type** Chromium-release assay  
**References** Kurane *et al.* 2003

- Three CD8+ CTL cell clones were derived from 2 HIV-1 positive asymptomatic patients, and their epitope specificities and HLA presenting proteins were defined.

**HXB2 Location** p24 (61–69)  
**Author Location** p24 (193–201 LAI)  
**Epitope** GHQAAMQML  
**Subtype** B

**Immunogen**  
**Species (MHC)** human (B39)  
**References** Kurane & West 1998

- Optimal peptide defined by titration.

**HXB2 Location** p24 (61–69)  
**Author Location**  
**Epitope** GHQAAMQML  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B39)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** supertype, cross-presentation by different HLA  
**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.

- In addition to its known HLA association (B39), 2 additional HLAs (A03, B38) were statistically predicted to be associated with this epitope.

**HXB2 Location** p24 (61–71)  
**Author Location** p24 (61–77)  
**Epitope** GHQAAMQMLKE  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, GHQAAMQMLKE, was detected within overlapping peptide GGHQAAMQMLKETINEEA.

**HXB2 Location** p24 (61–71)  
**Author Location** p24 (193–203 BRU)  
**Epitope** GHQAAMQMLKE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Claverie *et al.* 1988

- One of 4 epitopes first predicted, then shown to stimulate HLA-A2 restricted CTL line.

**HXB2 Location** p24 (61–71)  
**Author Location** p24 (61–70)  
**Epitope** GHQAAMQMLKE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 7/19 patients recognized this epitope.

**HXB2 Location** p24 (61–78)  
**Author Location** Gag

- Epitope** GHQAAMQMLKETINEEAA  
**Epitope name** GAG-27  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, immunodominance  
**References** Zhao *et al.* 2007
- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
  - 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
  - Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
  - 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
  - This peptide, GHQAAMQMLKeTINEEAA differs from the consensus C sequence GHQAAMQMLKdTINEEAA at 1 amino acid position, i.e. by 5.6%.

- HXB2 Location** p24 (61–80)  
**Author Location** p24 (193–212 SF2)  
**Epitope** GHQAAMQMKETINEEAAEW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997a
- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
  - Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
  - One of these 12 had CTL response to this peptide.
  - The responding subject was HLA-A26, A30, B38.

- HXB2 Location** p24 (61–82)  
**Author Location** p24 (193–214 BH10)  
**Epitope** GHQAAMQMLKETINEEAAEWDR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B52)  
**References** Johnson *et al.* 1991
- Gag CTL response studied in three individuals.

- HXB2 Location** p24 (62–70)  
**Author Location** Gag (Henan isolate)  
**Epitope** HQAAMQMLK  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006
- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

- HXB2 Location** p24 (62–70)  
**Author Location** p24 (194–202 LAI)  
**Epitope** HQAAMQMLK  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (B52)  
**References** Brander & Walker 1996
- P. Goulder, pers. comm.

- HXB2 Location** p24 (64–80)  
**Author Location** p24 (63–80 HXB2)  
**Epitope** AAMQMLKETINEEAAEW  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** T-cell Elispot  
**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment  
**References** Addo *et al.* 2003
- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
  - 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
  - A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
  - The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
  - Responses to this peptide were detected in 22% of the study subjects, and it was one of the 25 most frequently recognized peptides.

- HXB2 Location** p24 (65–72)  
**Author Location** p24

**Epitope** AMQMLKETI**Epitope name** A9I**Immunogen** vaccine*Vector/Type:* DNA *HIV component:* Gag**Species (MHC)** mouse (H-2<sup>d</sup>)**Assay type** Chromium-release assay**References** Bojak *et al.* 2002b

- Codon-optimized gag gene DNA vaccines were compared to wild type by vaccination of BALB/c mice. Codon optimized DNA gave a Th1 polarized Th response, a strong antibody response that persisted from more than 20 weeks, and CTL responses, while wild-type DNA induced weak and inconsistent immune responses.

**HXB2 Location** p24 (65–73)**Author Location** Gag (197–205 BRU)**Epitope** AMQMLKETI**Subtype** B, CRF02\_AG**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** Cote D'Ivoire**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 1/9 CRF02\_AG-infected Ivoirians, and 1/9 B-infected French subjects.

**HXB2 Location** p24 (65–73)**Author Location** Gag (199–207 HXB2)**Epitope** AMQMLKETI**Subtype** B**Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade HXB2*HIV component:* Gag**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Qiu *et al.* 1999

- Different expression vectors were tested to increase Gag expression in cell lines and create suitable vectors for DNA vaccines.
- Stable Gag expression was achieved in murine p815 cells, using a Gag gene that had mutated silent base positions that disrupt inhibitory RNA sequences which promote RNA degradation.
- Silent mutations were more effective than introduction of the D retrovirus cis-acting posttranscriptional control element (CTE) for enhancing Gag expression.
- The gag vector with silent mutations given as a vaccine to BALB/c mice gave CTL responses in splenic mononuclear cells, using peptide pulsed cells as targets.

**HXB2 Location** p24 (65–73)**Author Location** p24 (199–207 SF2)**Epitope** AMQMLKETI**Epitope name** p7g**Immunogen** vaccine*Vector/Type:* protein, vaccinia *Strain:* B clade SF2 *HIV component:* Gag, Gag-Pol *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Neidleman *et al.* 2000

- Intranasal immunization of CB6F1 (H2bxd) mice with soluble gag p55 with LT ADP-ribosyltransferase mutants (LTK63 and LTK73) from *Escherichia coli* as adjuvants was tested.
- Intranasal and intramucosal immunization of p55 gag protein with LTK63 or LTK72 adjuvant induced a CTL response comparable to intramuscular immunization responses.
- Oral co-administration of LTR72, with residual ADP-ribosyltransferase activity, induced systemic CTL responses, but LTK63 with no ADP-ribosyltransferase activity did not.

**HXB2 Location** p24 (65–73)**Author Location** p24 (66–74)**Epitope** AMQMLKETI**Immunogen** vaccine*Vector/Type:* DNA *HIV component:* Gag*Adjuvant:* vesicular stomatitis virus glycoprotein (VSV-G)**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Marsac *et al.* 2002

- BALB/c mice were injected with plasmids expressing HIV-1 Gag with or without coinjection of a plasmid expressing vesicular stomatitis virus glycoprotein (VSV-G). The combination encodes VSV-G pseudotyped Gag particles that can be taken up by cells for presentation in either the class I or class II pathways, while exogenous Gag alone can only be taken into the class II pathway.
- Vaccination with DNA expressing VSV-G pseudotyped Gag particles rather than just Gag increase Gag-specific CTL responses generally as well as the specific H-2d restricted anti-AMQMLKETI response.

**HXB2 Location** p24 (65–73)**Author Location** Gag**Epitope** ANQMLKDTI**Subtype** C**Immunogen** vaccine*Vector/Type:* DNA with CMV promotor*HIV component:* Gag, Protease**Species (MHC)** mouse (H-2<sup>d</sup>)**Country** India**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Cytolytic LDH release assay**Keywords** subtype comparisons, vaccine-induced epitopes, Th1**References** Chugh & Seth 2004

- A gag-protease gene construct from HIV-1 subtype C Indian strain has been shown to be successful in evoking immune responses to gag epitopes from both CD4+ and CD8+ T-cells in BALB/c mice. The immune response was of TH1 type. Recognition of seven Gag peptides carrying multiple epitopes indicates a broad-based immune response.



- A cross-clade response to the C clade epitope ANQMLKDTI was observed to the B clade version of this epitope, aNqm-lkEti. 66% lysis was observed to the peptide carrying the C clade epitope, only 33% to the B clade variant.

**HXB2 Location** p24 (65–73)

**Author Location** p24 (199–207 SF2)

**Epitope** AMQMLKETI

**Epitope name** p7G

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF2  
*HIV component:* Gag *Adjuvant:* DDA, DOTAP, CpG immunostimulatory sequence (ISS), MF59, PLG, urea

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**Keywords** dendritic cells

**References** O'Hagan *et al.* 2002

- Intramuscular or intraperitoneal immunization of BALB/c or CB6F1 mice with urea-solubilized, emulsified, or PLG-microparticle associated p55 Gag was studied in conjunction with the adjuvant CpG. CpG did not enhance CTL immunity when combined with urea solubilized p55, but did when combined with emulsions and PLG-microparticle antigen.
- CpG shifted the Ab response towards a IgG2a, and CpG was shown to upregulate CD86 on mouse bone-marrow derived dendritic cells.

**HXB2 Location** p24 (65–73)

**Author Location** p24 (199–207 SF2)

**Epitope** AMQMLKETI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor  
*Strain:* B clade SF2 *HIV component:* Gag, gp120

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Assay type** Chromium-release assay

**Keywords** epitope processing, vaccine-induced epitopes

**References** Doe *et al.* 1996

- Spleen cells from mice with distinct MHC types were infused into HIV vaccinated scid mice, to study the antigen presenting cells used by CTL induced in intramuscular injections. Bone marrow derived cells are used for presentation, but DNA infection is not required for priming, rather APCs can present proteins synthesized in other host cells.

**HXB2 Location** p24 (65–73)

**Author Location** p24 (199–207 SF2)

**Epitope** AMQMLKETI

**Immunogen** vaccine

*Vector/Type:* vaccinia *HIV component:* Gag, Pol

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**Keywords** immunodominance

**References** Doe & Walker 1996

- Immunodominant murine CTL response to this peptide observed after immunization with vaccine VVgagpol.
- Optimal peptide was defined.

**HXB2 Location** p24 (65–73)

**Author Location** Gag (197–205)

**Epitope** AMQMLKETI

**Immunogen** vaccine

*Vector/Type:* Listeria monocytogenes *HIV component:* Gag

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**References** Rayevskaya & Frankel 2001

- BALB/c mice were immunized with a highly attenuated recombinant Listeria monocytogenes, Lmdaldat, that can grow only when supplemented with D-alanine, and that expresses HIV-1 HXB2 Gag.
- Parenteral immunization provided protection against systemic and mucosal challenges with a recombinant vaccinia virus expressing HIV-1 gag, and a long lasting memory CTL response against Gag in spleen, mesenteric lymph nodes, and Peyer's patches directed against the gag protein.
- Oral immunization gave protection only against mucosal virus challenge and was associated with a transient CTL response in the three lymphoid tissues examined.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways.

**HXB2 Location** p24 (65–73)

**Author Location** Gag (197–205 SF2)

**Epitope** AMQMLKETI

**Immunogen** vaccine

*Vector/Type:* Listeria monocytogenes  
*Strain:* B clade HXB2 *HIV component:* Gag

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**Keywords** immunodominance

**References** Mata *et al.* 1998

- BALB/c mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways.
- This is the immunodominant CTL epitope in Gag in BALB/c mice.
- AMQMLKETI does not contain established Kd anchoring residue in position 2, tyrosine or phenylalanine, thus deviating from the typical Kd anchoring motif – the lack of the aromatic anchor residue is compensated for by interaction of the glutamine at P3 with pocket D of Kd.

**HXB2 Location** p24 (65–73)

**Author Location** Gag (HXB2)

**Epitope** AMQMLKETI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vaccinia, vesicular stomatitis virus (VSV) *Strain:* B clade HXB2, B clade IIIB *HIV component:* Env, Gag

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**Keywords** immunodominance

**References** Haglund *et al.* 2002a

- Different HIV strains were used for different regions: Env IIIIB, Gag HXB2.
- BALB/c mice were vaccinated with rec vesicular stomatitis virus (rVSV) expressing either HIV-1 Gag, Env, or both, and compared to using rec Env and Gag in vaccinia virus (rVVs). The primary response was determined by cell lysis, cytokine production and tetramer staining.
- Primary CTL responses to the immunodominant Gag (AMQMLKETI) epitope peaked in 7 days for GAG-rVSV, 3% of the cells were tetramer positive, and this response was 8-fold higher than for Gag-rVV.
- Vaccinating with GagEnv-rVSV carrying both Gag and Env allowed recognition of both HIV-1 proteins, but at reduced levels compared to either Gag-rVSV or Env-rVSV alone.
- Intranasal immunization with Env-rVSV yielded CTL responses that were strong but reduced compared to an intraperitoneal route.

**HXB2 Location** p24 (65–73)

**Author Location** Gag (HXB2)

**Epitope** AMQMLKETI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vaccinia, vesicular stomatitis virus (VSV) *Strain:* B clade HXB2, B clade IIIIB *HIV component:* Env, Gag

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**Keywords** immunodominance

**References** Haglund *et al.* 2002b

- Different HIV strains were used for different regions: Env IIIIB, Gag HXB2.
- BALB/c mice were vaccinated with rec vesicular stomatitis virus (rVSV) expressing either HIV-1 Gag or Env, or both, and retention of memory responses and recall responses were studied by tetramer staining and IFN-gamma production.
- Seven months after vaccination with Env-rVSV, 6% of the CD8+ cells were tetramer positive for the immunodominant Env epitope; these cells had a memory phenotype, CD44-Hi positive.
- Env in rec vaccinia virus (Env-rVV) elicited a strong recall response, with up to 45% of the CD8+ T-cell population tetramer positive and activated (expressing CD62L-Lo), and capable of IFN-gamma production.
- A prime with Env-rVSV and heterologous boost of Env-rVV gave remarkably high levels of memory cells, with approximately 1/3 of the CD8+ splenocytes being Env specific memory cells 150 days after the boost.
- A Gag-rVSV or EnvGag-rVSV prime and with a heterologous Gag-rVV or EnvGag-rVV boost combination gave 40% tetramer positive CD8+ cells, but the fraction of IFN-gamma producing cells was only about 25%. Still the heterologous vector prime-boost combination showed a profound benefit.
- A HIV-1 protein rVSV prime, rVV boost was a more potent combination than a vector reversal of a rVV prime and rVSV boost.

**HXB2 Location** p24 (65–73)

**Author Location** Gag

**Epitope** AMQMLKETI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* Listeria monocytogenes *HIV component:* Gag

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**Donor MHC** H-2d

**Assay type** Tetramer binding, Intracellular cytokine staining

**Keywords** genital and mucosal immunity

**References** Peters *et al.* 2003

- Intravenous, rectal, and oral vaccination of recombinant L. monocytogenes expressing HIV-1 Gag antigen were compared for their ability to stimulate a mucosal CTL response; mucosal administration of this vaccine gave strong mucosal response that was readily boosted.
- This CTL epitope is the immunodominant epitope in Gag for BALB/c mice, and was used to characterize the vaccine responses.

**HXB2 Location** p24 (65–73)

**Author Location** Gag (197–205)

**Epitope** AMQMLKETI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vaccinia, Listeria monocytogenes *HIV component:* Gag, Nef

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**Donor MHC** H-2d

**Assay type** Cytokine production, proliferation, Tetramer binding, Intracellular cytokine staining, Chromium-release assay

**Keywords** memory cells

**References** Rayevskaya *et al.* 2003

- Splenocytes derived from BALB/c mice immunized and boosted with Lmdd-gag were stimulated with gag-peptide specific antigen *in vitro*. In culture, CTL activity against this epitope reached a maximum at 9 days, then declined. Peptide restimulation gave a delayed (18 hours) but potent response, and growth was IL-2 or IL-15 dependent. Adoptive transfer of 5000 of the sorting purified cells could protect recipient BALB/c against vaccinia-gag challenge up to 3 months after transfer.

**HXB2 Location** p24 (65–73)

**Author Location**

**Epitope** AMQMLKETI

**Epitope name** A9I

**Immunogen** vaccine

*Vector/Type:* DNA, virus-like particle (VLP), polyepitope *HIV component:* Gag, p24 Gag, V3

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**Assay type** Cytokine production, Chromium-release assay

**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance, vaccine antigen design

**References** Wild *et al.* 2004

- A codon optimized gag DNA vaccine was compared to a myristylation defective gag and p24 alone, both of which lack signals for secretion from transfected cells. Gag-derived immunogens that were secreted as VLPs and those that remained intracellular (p24) each produced strong CTL responses, and neither the size of antigen nor cellular trafficking and localization significantly influenced the strength of humoral and cellular immune activation. The formation and release of VLPs was not essential for eliciting strong CTL. BALB/c mice were given the DNA vaccine by i.m. administration of plasmid DNA for the prime and boost.
- Linking the region encoding the V3 immunodominant epitope to the gag gene did not diminish the response to the Gag p24 epitope A9I, but did enable a response to the V3 epitope.
- Minigenes were made incorporating just 1 epitope, minitopes, carrying 1 of 3 murine class I epitopes linked to the Ad2-E3 protein-derived signal peptide to allow access of the epitope to the ER. Weak induction of cellular immune responses was observed, in contrast to the complex polyprotein.

**HXB2 Location** p24 (65–73)  
**Author Location** Gag (197–205)  
**Epitope** AMQMLKETI  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade HXB2 *HIV component:* Gag  
**Species (MHC)** mouse (H-2K<sup>d</sup>)  
**Country** United States  
**Assay type** proliferation, T-cell Elispot  
**Keywords** vaccine antigen design  
**References** Kwak *et al.* 2004

- A recombinant vaccinia virus with HIV-1 Gag replacing the cytoplasmic domain of the B5R protein was shown to induce better primary CD4 response than recombinant vaccinia virus expressing Gag from the TK-locus; CD8 responses were less specific. When immunized BALB/c mice were challenged with a recombinant *Listeria* that expresses HIV-Gag, lower colony counts of *Listeria* were found in the liver and spleen of mice immunized with virus expressing B5R-Gag fusion protein.

**HXB2 Location** p24 (65–73)  
**Author Location** Gag  
**Epitope** AMQMLKDTI  
**Epitope name** G  
**Subtype** A, B, C  
**Immunogen** vaccine  
*Vector/Type:* DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT  
**Species (MHC)** mouse (H-2K<sup>d</sup>)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism  
**References** Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
- After immunization with Clades A or C vaccines, both containing Epitope G, AMQMLKDTI, T cells responded well to this index epitope, but poorly to Clade B variant AMQMLKeTI, and intermediately to variant AMQiLKDTI. Induction by Clade B vaccine, containing epitope AMQMLKETI, generated good responses to both Clade B and A variants, but not to variant AMQiLKDTI.

**HXB2 Location** p24 (65–73)  
**Author Location** Gag (C-96BW04.09)  
**Epitope** AMQMLKDTI  
**Epitope name** A  
**Subtype** C  
**Immunogen** vaccine  
*Vector/Type:* DNA, alphavirus replicon  
*Strain:* C clade C-96BW04.09, C clade C-96BW15C05 *HIV component:* Gag, Gag-Pol, Pol  
**Species (MHC)** mouse (H-2d)  
**Assay type** Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes, vaccine antigen design  
**References** Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- AMQMLKDTI has a previously identified B clade homolog AMQMLKeTI.

**HXB2 Location** p24 (65–73)  
**Author Location** Gag  
**Epitope** AMQMLKETI  
**Subtype** A, B  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* A clade, B clade  
*HIV component:* Env, Gag  
**Species (MHC)** mouse (H-2d)  
**Country** Finland  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** vaccine antigen design  
**References** Malm *et al.* 2007

- A novel mouse model was used to test the efficacy of 2 HIV DNA vaccines in protection against tumor challenge. Comparable immunogenicity between the single and multi-clade vaccines tested was seen in different mouse strains. CTL response to HIV-1-APCs was both in vivo and in vitro and this animal model not only evaluated vaccine immunogenicity but also confirmed the potency of GTU-multi-HIV vaccines.

- HXB2 Location** p24 (65–73)  
**Author Location** Gag (199–207)  
**Epitope** AMQMLKETI  
**Epitope name** p7g  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* vaccinia, Sindbis *HIV component:* Gag
- Species (MHC)** mouse  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** genital and mucosal immunity  
**References** Vajdy *et al.* 2001
- Nasal, vaginal, rectal and i.m. immunization was performed with Sindbis virus expressing HIV-1 Gag (SIN-Gag), followed by intravaginal or intrarectal challenge with vaccinia virus expressing either Gag (VV-Gag) or gp160 (VV-gp160) as a control.
  - Intranasal and intramuscular immunization followed by intravaginal challenge induced HIV-1 Gag specific, IFN- $\gamma$  producing CD8+ T-cells in the vaginal/uterine mucosal tissue, as well as in the draining iliac lymph nodes and in the spleen, but could not protect against a VV-Gag infection of the ovaries. Local vaginal or rectal immunization, despite lower CD8+ T-cell responses, did provide protection.

- HXB2 Location** p24 (65–73)  
**Author Location** Gag (Du422)  
**Epitope** AMQMLKDTI  
**Subtype** C  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* C clade Du422  
*HIV component:* Gag
- Species (MHC)** mouse  
**Donor MHC** H-2d  
**Assay type** Chromium-release assay  
**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization  
**References** van Harmelen *et al.* 2003
- The pTHgagC DNA vaccine employed in this study expressed the gag gene derived from the South African isolate Du422, which was selected on the basis of being the natural strain most similar to the South African subtype C consensus sequence (aa distance of 1.8%).
  - A E7D mutation was introduced into the epitope to match the gag subtype C sequence in the vaccine. Mice vaccinated with the gag DNA made strong CTL responses against AMQMLKDTI, boosting enhanced the response, and memory cells persisted for 15 weeks.

- HXB2 Location** p24 (65–73)  
**Author Location** p24 (197–205)  
**Epitope** AMQMLKETI?  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Gag  
*Adjuvant:* Cholera toxin (CT)
- Species (MHC)** mouse  
**Donor MHC** H-2d  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay  
**Keywords** TCR usage, genital and mucosal immunity

- References** Yoshizawa *et al.* 2003
- Intranasal immunization triggered CTL response in the nasal-associated lymphoid tissue (NALT), posterior cervical lymph nodes (pCLNs) and the spleen, but not in the mesenteric lymph nodes (MLNs). Rectal immunization elicited CTL responses only in the MLNs. By immunizing mice nasally following rectal immunization, CTL responses were detected in NALT, pCLNs, spleen and MLNs. Epitope-specific CD8+ T-cells were primarily located in NALT after 6 days and in pCLNs after 2 months.
  - The strongest specific lysis was induced by NALT-specific CTL clones. pCLNs derived memory CTL clones originated from NALT CTL clones, as determined by T-cell receptor V $\beta$  usage.

- HXB2 Location** p24 (69–86)  
**Author Location** (C consensus)  
**Epitope** LKDTINEEAAEWDRHPV  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*6801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- HXB2 Location** p24 (69–86)  
**Author Location** Gag (201–218 LAI)  
**Epitope** LKETINEEAAEWDRVPV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Buseyne *et al.* 1993a
- Vertical transmission of HIV ranges from 13% to 39%.
  - Primary assays showed that cytotoxic activity against at least one HIV protein detected in 70% of infected children.
  - Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
  - Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag.

- HXB2 Location** p24 (69–86)  
**Author Location** Gag  
**Epitope** LKETINEEAAEWDRHPV  
**Epitope name** GAG-28  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, immunodominance  
**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, LKeTINEEAAEWDR LHPV differs from the consensus C sequence LKdTINEEAAEWDR LHPV at 1 amino acid position, i.e. by 5.6%.

**HXB2 Location** p24 (70–78)

**Author Location** p24 (70–78)

**Epitope** KETINEEAA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*404)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, KETINEEAA, was detected within overlapping peptideS GGHQAAMQMLKETINEEA, LKETINEEAAEWDR LHPV and AAEWDR LHPVHAGPIA.

**HXB2 Location** p24 (70–78)

**Author Location**

**Epitope** KETINEEAA

**Epitope name** Gag-KA9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4002)

**Donor MHC** 01RCH46: A\*0201, A\*0217, B\*0801, B\*4002, Cw\*0303, Cw\*0701

**Keywords** HAART, ART

**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 01RCH46 was Hispanic, on HAART, and had a viral load of 21000 and CD4 count of 623 – she also recognized GELDRWEKI, p17(11-19), HLA B\*4002, and TAFTIPSI, RT(128-135), HLA A\*0217.
- Among HIV+ individuals who carried HLA B40, 3/5 (60%) recognized this epitope.

**HXB2 Location** p24 (70–78)

**Author Location** p24 (70–78)

**Epitope** KETINEEAA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4002)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** p24 (71–80)

**Author Location**

**Epitope** ETINEEAAEW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*25)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** characterizing CD8+ T cells

**References** Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.
- A\*25-restricted epitope ETINEEAAEW does not correlate with any particular CTL maturation phenotype.

**HXB2 Location** p24 (71–80)

**Author Location** p24 (203–212)

**Epitope** ETINEEAAEW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2501)

**Keywords** subtype comparisons

**References** Klenerman *et al.* 1996

- The epitope was defined through direct stimulation of PBMC with 20-mer peptides.
- It is in a conserved region, ETINEEAAEW is found in most B, D, and E subtype isolates.
- DTINEEAAEW is found in A and some D subtype sequences.

**HXB2 Location** p24 (71–80)

**Author Location** p24 (203–212)

**Epitope** ETINEEAAEW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*2501 epitope.

**HXB2 Location** p24 (71–80)

**Author Location** p24 (203–212)

**Epitope** ETINEEAAEW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2501)

**References** van Baalen *et al.* 1996

- Conserved between B and D subtypes, variable in other clades; a consensus of clades A, C, F, G, and H and a peptide of HIV-2ROD over this region were not recognized by CTL recognizing the index peptide.
- C. Brander notes that this is an A\*2501 epitope in the 1999 database.

**HXB2 Location** p24 (71–80)

**Author Location** p24 (71–80 HXB2)

**Epitope** ETINEEAAEW

**Epitope name** EW10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2501)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- ETINdEAAEW CTL escape mutant elicited a reduced CTL response.

**HXB2 Location** p24 (71–80)

**Author Location** p24

**Epitope** ETINEEAAEW

**Immunogen**

**Species (MHC)** human (A25)

**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: EIINEEAAEW, no cross-reactivity van Baalen *et al.* [1996]

**HXB2 Location** p24 (71–80)

**Author Location** p24 (203–212 SF2)

**Epitope** ETINEEAAEW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A25)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A25+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/2 group 2, and 1/3 group 3.

**HXB2 Location** p24 (71–80)

**Author Location** p24 (202–211)

**Epitope** ETINEEAAEW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A25)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** Th1, characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8+ cells are found, each one constituting 30-40% of the CD8+ cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- 1/3 patients responded to this peptide with GzB producing cells, and the other two responded with IFN-gamma producing cells.

**HXB2 Location** p24 (71–80)

**Author Location**

**Epitope** ETINEEAAEW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A25)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope ETINEEAAEW elicited a magnitude of response of 380 SFC with a functional avidity of 0.005nM.

**HXB2 Location** p24 (71–80)

**Author Location**

**Epitope** DTINEEAAEW

**Epitope name** Gag-DW10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5301)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B\*5301, 2/15 (13%) recognized this epitope.

**HXB2 Location** p24 (71–80)

**Author Location**

**Epitope** ETINEEAAEW

**Epitope name** Gag-EW10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5301)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B\*5301, 2/15 (13%) recognized this epitope.

**HXB2 Location** p24 (71–80)

**Author Location** p24 (71–80)

**Epitope** DTINEEAAEW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.

- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope DTINEEAAEW is highly conserved across clades, >70% to clades A and C.

**HXB2 Location** p24 (71–80)

**Author Location** p24 (203–212)

**Epitope** DTINEEAAEW

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B53)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B53 women, 0/2 HEPS and 7/9 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 4 of the 7/9 responsive HIV-1 infected women.

**HXB2 Location** p24 (71–80)

**Author Location** p24 (203–212 subtype A consensus)

**Epitope** DTINEEAAEW

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Keywords** binding affinity, subtype comparisons, epitope processing

**References** Dorrell *et al.* 2001

- In clade A infected Gambians, three HLA-B53 epitopes were defined in Gag p24 using ELISPOT, tetramer, and cytotoxicity assays.
- Two of the new epitopes lacked the predicted P2 anchors, DTINEEAAEW and QATQEVKNM, and bound to B53 with high affinity, thus extending the anchor residue motif for B53 and the related B35.
- Two overlapping 20 mer peptides carry this complete epitope, but only one stimulates recognition, which could be due to different peptide processing.
- DTINEEAAEW was recognized in only 2/7 HLA-B53 subjects.
- DTINEEAAEW was not A subtype specific and there was cross-recognition although diminished, of the subtype B, C, and D variant, ETINEEAAEW.
- In one of the two subjects there was cross-recognition of the HIV-2 version of the epitope, EIINEEAADW.

**HXB2 Location** p24 (71–80)

**Author Location** p24

- Epitope** ETINEEAAEW  
**Subtype** A, B, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B53, B58)  
**Donor MHC** A36, A74, B53, B58, Cw4, Cw6; A23, A34, B44, B53, Cw4, Cw6; A23, A24, B35, B58, Cw4, Cw7  
**Country** Democratic Republic of the Congo  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization  
**References** Geels *et al.* 2005
- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
  - This previously described B53 epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype A Gag. The autologous epitope sequence in this person differed from the known epitope by one amino acid, E1D, dTINEEAAEW. It was also recognized in a person carrying a subtype D gag, and in this case the autologous sequence matched the epitope. This was also predicted to possibly be a B58 cross-presented epitope in another subtype D Gag infected person based on peptide reactivity and a known B58 motif.

- HXB2 Location** p24 (71–80)  
**Author Location**  
**Epitope** ETINEEAAEW  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN  
*HIV component:* Gag-Pol, gp120, gp41  
**Species (MHC)** human  
**Donor MHC** A\*2501, A\*3002; B\*0702, B\*1801  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes  
**References** Horton *et al.* 2006b
- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
  - None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
  - Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
  - This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

- HXB2 Location** p24 (71–90)  
**Author Location** p24 (203–222 SF2)  
**Epitope** ETINEEAAEWDRVHPVVHAGP  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997a
- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
  - Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
  - One of these 12 had CTL response to this peptide.
  - The responding subject was HLA-A2, B21.

- HXB2 Location** p24 (75–83)  
**Author Location** Gag (207–215)  
**Epitope** EEAAEWDV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*40)  
**Donor MHC** A\*03, A\*24, B\*35, B\*40  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** acute/early infection, variant cross-recognition or cross-neutralization, superinfection  
**References** Yang *et al.* 2005b
- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
  - The response to the epitope EEAAEWDV was found in the patient before superinfection and diminished afterwards; the initial infecting and superinfecting strain carried EEAAEWDRI.

- HXB2 Location** p24 (77–87)  
**Author Location** Gag (216–226)  
**Epitope** AAEDRLHPVH  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005
- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
  - 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.



**HXB2 Location** p24 (77–92)  
**Author Location** p24  
**Epitope** AAEDRLHPVHAGPIA  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J. Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, AAEDRLHPVHAGPIA, had an overall frequency of recognition of 20% - 18.6% AA, 23.1% C, 25% H, 9.5% WI. This peptide is included in a 41 aa Gag-p17 highly reactive region to be used for vaccine design.

**HXB2 Location** p24 (78–86)  
**Author Location** p24 (78–86)  
**Epitope** AEWDLHPV  
**Epitope name** AEW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, escape  
**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relative efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive epitopes found not to vary over time.

**HXB2 Location** p24 (78–86)  
**Author Location** p24 (Henan isolate)  
**Epitope** AEWDLHPV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- AEWDLHPV was among 5 mostly recognized epitopes (69%).

**HXB2 Location** p24 (78–86)  
**Author Location** p24 (78–86)  
**Epitope** AEWDLHPV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*04)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.

- This epitope, AEWDRLHPV, was detected within overlapping peptides LKETINEEAAEWDRHPV and AAEWDRHPVHAGPIA.

**HXB2 Location** p24 (78–86)  
**Author Location** Gag (210–218)  
**Epitope** AEWDRVHPV  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*40)  
**Donor MHC** A\*03, A\*24, B\*35, B\*40  
**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** acute/early infection, variant cross-recognition or cross-neutralization, superinfection

**References** Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- The epitope AEWDRVHPV was recognized in the patient before superinfection and diminished afterwards. The initial and superinfecting strains had the variant AEWDRIHPV.

**HXB2 Location** p24 (78–86)  
**Author Location**

**Epitope** AEWDRVHPV  
**Epitope name** Gag-AV9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4002)  
**Donor MHC** A\*0201, A\*3201, B\*4002, B\*5301, Cw\*0202, Cw\*0401

**Keywords** HAART, ART  
**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 01RCH59 was Hispanic, not on HAART, and had a viral load of 5100 and CD4 count of 349 – she also recognized TERQANFL, p2p7p1p6(64–71), HLA-B\*4002, and KEKG-GLEGL, Nef(92–100), HLA-B\*4002.
- Among HIV+ individuals who carried HLA B40, 4/5 (80%) recognized this epitope.

**HXB2 Location** p24 (78–86)  
**Author Location** p24 (78–86)

**Epitope** AEWDRVHPV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4002)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** p24 (78–86)  
**Author Location** p24 (78–86)  
**Epitope** AEWDRLHPV  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4006, Cw\*0602)  
**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope AEWDRLHPV showed >50% conservation across clades with >90% to subtype D.

**HXB2 Location** p24 (81–91)  
**Author Location** Gag (213–223)  
**Epitope** DRVHPVHAGPI

**Epitope name** Gag 11.4  
**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade  
*HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu

**Species (MHC)** macaque  
**Assay type** T-cell Elispot, Intracellular cytokine staining  
**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization, memory cells

**References** Amara *et al.* 2005

- A clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better conserved for CD8 than CD4 T cells.
- All 5 CD8 and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. The similar reported human epitope in this case is VHPVHAGPIA, restricted by HLA B55.

- 3 of 5 CD8 epitopes and 2 of 8 CD4 epitopes were conserved across multiple HIV-1 clades. DRVHPVHAGPI is identical in HXB2 and the CRF02 consensus. It is relatively conserved across other clades, but usually has an L in the third position: DRIHPVHAGPI.

- HXB2 Location** p24 (81–100)  
**Author Location** p24 (81–100)  
**Epitope** DRLHPVHAGPAAPGQMRPR  
**Epitope name** DRL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, escape  
**References** Oxenius *et al.* 2004b
- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0–80% as efficiently as the index peptide, and the relative efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
  - This epitope was not precisely defined, but was one of six epitopes found to be under positive selection for escape mutations and was completely replaced by escape variants between days 66 and 327 (drlhphvtagplapqmrpr).

- HXB2 Location** p24 (82–92)  
**Author Location** Gag (217–227)  
**Epitope** RLHPVHAGPIA  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005
- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
  - 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

- HXB2 Location** p24 (83–91)  
**Author Location** Gag (215–223)  
**Epitope** LHPVHAGPI  
**Subtype** B  
**Immunogen** HIV-1 infection, peptide-HLA interaction

- Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** immunodominance  
**References** Rolland *et al.* 2007b
- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
  - Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
  - This HIV-1 epitope, LHPVHAGPI, is similar to human protein PTPRE, sequence LnPVHAGPIV and human protein T cell leukemia Homeobox 1, sequence LHPgHAePIV.

- HXB2 Location** p24 (83–92)  
**Author Location** p24 (215–223 IIIB)  
**Epitope** VHPVHAGPIA  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B55)  
**References** Sipsas *et al.* 1997
- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
  - LHPVHAGPVA, a variant found in HIV-1 PH136, was also recognized.
  - LHPVHAGPIA, a variant found in HIV-1 RF, was also recognized.
  - LHPVHAGPIT, a variant found in HIV-1 MN, was also recognized.
  - LHPAQAGPIA, a variant found in HIV-1 JH3, was recognized at high peptide concentrations.

- HXB2 Location** p24 (83–92)  
**Author Location** Gag (215–224)  
**Epitope** VHPVHAGPIA  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B55)  
**Donor MHC** A11, A24, B55, B56  
**Country** United Kingdom  
**Assay type** Flow cytometric T-cell cytokine assay, Other  
**Keywords** HAART, ART, immunodominance, TCR usage, memory cells  
**References** Weekes *et al.* 2006
- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintenance of such strong functional responses

implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

**HXB2 Location** p24 (84–91)

**Author Location** p24

**Epitope** HPVHAGPI

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p24 (84–92)

**Author Location** (C consensus)

**Epitope** HPVHAGPIA

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3910)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HPVHAGPIA is an optimal epitope.

**HXB2 Location** p24 (84–92)

**Author Location**

**Epitope** HPVHAGPIA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B07)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.

- In addition to its known HLA association (B07), an additional HLA (B55) was statistically predicted to be associated with this epitope.

**HXB2 Location** p24 (84–92)

**Author Location** (C consensus)

**Epitope** HPVHAGPIA

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (84–92)

**Author Location** (C consensus)

**Epitope** HPVHAGPIA

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HPVHAGPIA is an optimal epitope.

**HXB2 Location** p24 (84–92)

**Author Location** p24 (84–92)

**Epitope** HPVHAGPIA

**Epitope name** B7-HA9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection—10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 3/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** p24 (84–92)

**Author Location** p24 (84–92)

**Epitope** HPVHAGPIA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** p24 (84–92)

**Author Location** p24 (84–92)

**Epitope** HPVHAGPVA

**Epitope name** B7-HA9 Gag

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The first infecting strain had the variant hpvhagpIa. The CTL response was higher to the second superinfecting variant, HPVHAGPVA.

**HXB2 Location** p24 (84–92)

**Author Location** (B consensus)

**Epitope** HPVHAGPVA

**Epitope name** HA9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A03, B07, Cw7

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** p24 (84–92)

**Author Location** Gag (216–224)

**Epitope** HPVHAGPIA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** p24 (84–92)

**Author Location** Gag

**Epitope** HPVHAGPIA

**Epitope name** B7-HA9(Gag)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (84–100)

**Author Location** p24 (87–101)

**Epitope** HPVHAGPIAPGQMREPR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, HPVHAGPIAPGQMREPR, was detected within overlapping peptides LHPVHAGPIAPGQMREPR, LKETINEEAAEWDRHPV and AAEWDRHPVHAGPIA.

**HXB2 Location** p24 (87–101)

**Author Location** Gag

**Epitope** HAGPIAPGQMREPRG

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A\*02 restricted epitope, HAGPIAPGQMREPRG was mutated to qAGPIAPGQMREPRG in the daughter D2 isolate.

**HXB2 Location** p24 (87–101)

**Author Location** p24 (219–233 BRU)

**Epitope** HAGPIAPGQMREPRG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Claverie *et al.* 1988

- One of 4 epitopes predicted then shown to stimulate HLA-A2 restricted CTL line.

**HXB2 Location** p24 (87–101)

**Author Location** p24 (87–101)

**Epitope** HAGPIAPGQMREPRG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 19 patients recognized this epitope.

**HXB2 Location** p24 (87–101)

**Author Location** Gag (219–233 LAI)

**Epitope** HAGPIAPGQMREPRG

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag.

**HXB2 Location** p24 (89–96)

**Author Location** p24 (89–97)

**Epitope** GPIAPGQM

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance, optimal epitope

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be

recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.

- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope GPIAPGQM was novel and conserved across clades B, C and D.

**HXB2 Location** p24 (89–96)

**Author Location** p24

**Epitope** GPIAPGQM

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p24 (91–105)

**Author Location** (C consensus)

**Epitope** IAPGQMREPRGSDIA

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*13)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** p24 (91–110)

**Author Location** p24 (223–242 SF2)

**Epitope** IAPGQMREPRGSDIAGTTST

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.

- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A2, A24, B13, B35.

**HXB2 Location** p24 (93–107)

**Author Location** Gag (225–239)

**Epitope** PGQMREPRGSDIAGT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*03, A\*24, B\*35, B\*40

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, superinfection, characterizing CD8+ T cells

**References** Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- An early response to this peptide was detected that waned prior to superinfection. The embedded epitope and HLA presenting molecule were not resolved. The initial and superinfecting strains carried a perfect match to the peptide sequence.

**HXB2 Location** p24 (94–104)

**Author Location** Gag (226–236)

**Epitope** GQMREPRGSDI

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*13)

**Donor MHC** A\*0301, A\*3001, B\*1301, B\*1402, Cw\*0602, Cw\*0802

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism

**References** Honeyborne *et al.* 2007

- To determine whether HLA-B\*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B\*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B\*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.

**HXB2 Location** p24 (94–104)

**Author Location**

**Epitope** GQMREPRGSDI

**Epitope name** GI11**Immunogen****Species (MHC)** human (B13)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a B13 epitope.

**HXB2 Location** p24 (94–105)**Author Location** Gag (229–239)**Epitope** GQMREPRGSDIA**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Country** India**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** subtype comparisons**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p24 (101–120)**Author Location** p24 (233–252 SF2)**Epitope** GSDIAGTTSTLQEIQGWMTN**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A26, A30, B38.

**HXB2 Location** p24 (102–119)**Author Location** Gag (245–252)**Epitope** SDIAGTTSTVDEQIQWMY**Subtype** HIV-2**Immunogen** HIV-2 infection**Species (MHC)** human**Country** Guinea-Bissau**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other**Keywords** rate of progression, optimal epitope, HIV-2**References** Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most

recognized peptides were clustered in a highly conserved region of Gag.

- This peptide, SDIAGTTSTVDEQIQWMY, was recognized by 10 out of 65 subjects. It is found in the 149 amino-acid long HIV-2 proteome region of Gag 175-323.

**HXB2 Location** p24 (107–115)**Author Location** Gag (239–247 SF2)**Epitope** TTSTLQEIQ**Immunogen** vaccine*Vector/Type:* Listeria monocytogenes*Strain:* B clade HXB2 *HIV component:* Gag**Species (MHC)** mouse (H-2K<sup>d</sup>)**References** Mata *et al.* 1998

- BALB/c mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways.

**HXB2 Location** p24 (107–115)**Author Location** Gag**Epitope** TTSTLQEIQ**Epitope name** T**Subtype** A, B, C**Immunogen** vaccine*Vector/Type:* DNA with CMV promoter, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT**Species (MHC)** mouse (H-2K<sup>d</sup>)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other**Keywords** subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism**References** Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.

**HXB2 Location** p24 (108–117)**Author Location** Gag (241–249)**Epitope** TSTLQEIQGW**Epitope name** TW10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*310102, A\*6603, B\*440302, B\*570301, Cw\*040101, Cw\*07)**Country** United States



- Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other
- Keywords** escape, viral fitness and reversion, drug resistance
- References** Bailey *et al.* 2007
- In this study the entire HIV-1 genome was analyzed before and after virologic escape for the first time and escape mutations were temporarily associated with an increased viremia in an otherwise B\*57-elite controller of viral load. It is suggested that HLA-B\*57-restricted CTL mutations were the major cause of escape because other multiple drug resistance mutations in Pol and RT (M184V and T215Y) did not result in a marked increase in viral replication capacity in vitro.
  - CTLs detecting this Gag epitope, TSTLQEQIGW, were detectable and levels remained unchanged over 20 months. TW10 changed over time from TSTLQEQIaW to TSTLQEQIgW to TSTLQEQIeW to TSTLQEQIdW.

**HXB2 Location** p24 (108–117)

**Author Location** Gag

**Epitope** TSTLQEQIGW

**Epitope name** TW10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- Several mutations in this epitope were found to potentially act as CTL escape mutations. These are: E245D, G248E, and a triple mutation Q244T/I247V/G248A.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (108–118)

**Epitope** TSTLQEQIGW

**Epitope name** TW10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Country** United Kingdom, Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** TCR usage, structure, characterizing CD8+ T cells

**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFN-PEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (108–117)

**Epitope** TSTLQEQIGW

**Epitope name** TW10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57, B\*58)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, subtype comparisons, acute/early infection

**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this epitope, TW10 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen only to the C-clade variant. Anchor residues are at positions 2 and 10; while the A-clade variant contains a non-conservative change at position 4 to TSTpQE-QIGW, and the C-clade variant has a semi-conservative substitution at position 9 to TSTLQEQIaW. Reduced avidity was seen with the clade-C variant.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (108–117)

**Epitope** TSTLQEQIGW

**Epitope name** TW10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57, B\*58)

**Country** Switzerland

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** rate of progression, HLA associated polymorphism

**References** Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than "other" HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by "other", non-advantageous HLA I in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.

- Patients with higher proportions of mutated epitopes also showed lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variants TSnLQEQIGW and TSTLQEQIaW at positions 3 and 9, were present in 86.7% of HLA-matched patients and 28.3% of HLA-unmatched patients. Phylogenetic analysis identified the threonine at position 3 to be under strong positive selective pressure.

**HXB2 Location** p24 (108–117)

**Author Location** Gag (240–249)

**Epitope** TSTLQEQIGW

**Epitope name** TW10

**Immunogen** HIV-1 infection, in vitro stimulation or selection

**Species (MHC)** human (B\*57, B\*5801)

**Assay type** Other

**Keywords** escape, viral fitness and reversion

**References** Martínez-Picado *et al.* 2006

- Escape patterns of TSTLQEQIGW epitope were studied in 258 C-clade infected subjects from Durban, South Africa, and 187 B-clade infected subjects from diverse sources. 206 subjects were B\*57/5801-positive.
- TS[t/n]LQEQIGW (T242N) escape mutation was present in 153/206 of B\*57/5801-positive subjects and only in 2/239 B\*57/5801-negative subjects.
- TS[t/n]LQEQIGW (T242N) mutation reduced viral replicative capacity based on in-vitro growth competition assays, supporting the inference of a fitness cost of T242N mutation from observations of reversion in B\*57/5801-negative subjects.
- Structural analysis suggested a critical role for T in Gag 242 position in defining the start point and in stabilizing helix 6 with p24 Gag, explaining the significant cost of escape.
- TW10-associated mutations were found in Gag positions 248,250,252 and for each a strong association with a potential compensatory mutation(s) was identified.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (240–249 LAI)

**Epitope** TSTLQEQIGW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5701 epitope.

**HXB2 Location** p24 (108–117)

**Author Location**

**Epitope** TSTLQEQIGW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** rate of progression, immunodominance

**References** Migueles & Connors 2001

- HLA B\*5701 was found in a very high frequency in HIV-1 infected non-progressors, 11/13 (85%) versus 19/200 (9.5%) of progressors. Non-progressors tended to have an immune response that was highly focused on four p24 epitopes that were presented by B\*5701, ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.

**HXB2 Location** p24 (108–117)

**Author Location**

**Epitope** TSTLQEQIGW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** rate of progression, immunodominance

**References** Migueles & Connors 2001

- CTL activity was monitored in 27 individuals, including 10 LTNP with an over-expression of HLA B\*5701 – these individuals have viral loads below the threshold of infection without therapy, and their immune response tends to be focused on peptides that contain B\*5701 epitopes ISPRTLNAW, KAFSPEVIPMF, TSTLQEQIGW, and QASQEVKNW.
- CTL responses are broader in B\*5701+ individuals with progressive viremia than those that control viremia.
- The HLA-A\*0201 SLYNTVATL epitope response was not as strong in individuals that carried both A2, B57.

**HXB2 Location** p24 (108–117)

**Author Location**

**Epitope** TSTLQEQIGN

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Migueles *et al.* 2003

- cDNA Gag sequences from a set of 17 HLA-B\*5701+ progressors and 10 LTNPs were obtained, and the variation in four p24 B\*5701 epitopes examined. Sequence variants were more common ( $p < 0.01$ ) in the epitopes in the progressors (median 3, range 1-7) than LTNPs (median 2, range 0-4).
- In general, use of the autologous protein in a target cell did not diminish the overall CD8+ T-cell responses.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (1513–)

**Epitope** TSTLQEQIGW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Country** Australia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, HLA associated polymorphism

**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore *et al.*, Science 296:1439 2002) were found

to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.

- The third position of this epitope TStLQEIQGW has a mutational pattern that is correlated with the host carrying HLA B\*5701.

**HXB2 Location** p24 (108–117)  
**Author Location** p24 (108–117)  
**Epitope** TSTLQEIQGW  
**Epitope name** TST  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5701)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells  
**References** Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B57-TST (that is strongly associated with delayed progression to AIDS) and its alanine-substituted variants are efficiently cross-recognized.

**HXB2 Location** p24 (108–117)  
**Author Location** (108–117)  
**Epitope** TSTLQEIQAW  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5701, B\*5801)  
**Assay type** Other  
**Keywords** HLA associated polymorphism  
**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- TSTLQEIQAW was a previously defined B\*5701/B\*5801 presented epitope that encompassed a B\*57/B\*5801 associated polymorphism, TStLQEIQAW, in the third position.

**HXB2 Location** p24 (108–117)  
**Author Location** (C consensus)  
**Epitope** TSTLQEIQAW  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5703)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the T3 and A9 residues of TSTLQEIQAW are associated with the presence of the HLA presenting molecule in the host.
- TSTLQEIQAW is cross presented by both B\*5801 and B\*5703.

**HXB2 Location** p24 (108–117)  
**Author Location** Gag  
**Epitope** TSTLQEIQAW  
**Epitope name** TW10  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5703, B\*5801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** rate of progression, HLA associated polymorphism  
**References** Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than "other" HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by "other", non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also showed lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variant TSnLQEIQGW at position 3 was often found in conjunction with a second polymorphism at positions 5, 8 or 9.

**HXB2 Location** p24 (108–117)  
**Author Location** p24 (240–249 LAI)  
**Epitope** TSTLQEIQGW  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5801 epitope. Variant TSTveE-QqiW also noted.

**HXB2 Location** p24 (108–117)  
**Author Location** Gag (240–249)  
**Epitope** TSTVEEQIQW  
**Epitope name** TSTV  
**Subtype** HIV-2  
**Immunogen** HIV-2 infection  
**Species (MHC)** human (B\*5801)  
**Country** Gambia  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Flow cytometric T-cell cytokine assay  
**Keywords** characterizing CD8+ T cells, HIV-2  
**References** Gillespie *et al.* 2005

- CD8 T-cell responses were evaluated and compared in HIV-1 and HIV-2 infected individuals. A significantly greater magnitude and breadth of Gag-specific responses were found in HIV-1 infected individuals, possibly because of undetectable viral load in HIV-2 infected individuals. This finding suggests that responses in HIV-2 infection reflect antigen load in plasma, as is the case in HIV-1 infection. No correlation was found between immune control of HIV-2 and the frequency of perforin-expressing virus-specific CD8 T-cells.
- 4/5 HIV-2-infected B\*5801-positive subjects recognized TSTVEEQIQW, the HIV-2 version of this epitope. 0/4 HIV-1-infected B\*5801-positive subjects responded to TSTLQE-QIGW, the HIV-1 version of this epitope.

**HXB2 Location** p24 (108–117)  
**Author Location** Gag (240–249)  
**Epitope** TSTLQEIQGW  
**Epitope name** TSTL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5801)  
**Country** Gambia  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Flow cytometric T-cell cytokine assay  
**Keywords** characterizing CD8+ T cells, HIV-2  
**References** Gillespie *et al.* 2005

- CD8 T-cell responses were evaluated and compared in HIV-1 and HIV-2 infected individuals. A significantly greater magnitude and breadth of Gag-specific responses were found in HIV-1 infected individuals, possibly because of undetectable viral load in HIV-2 infected individuals. This finding suggests that responses in HIV-2 infection reflect antigen load in plasma, as is the case in HIV-1 infection. No correlation was found between immune control of HIV-2 and the frequency of perforin-expressing virus-specific CD8 T-cells.
- 4/5 HIV-2-infected B\*5801-positive subjects recognized TSTVEEQIQW, the HIV-2 version of this epitope. 0/4 HIV-1-infected B\*5801-positive subjects responded to TSTLQE-QIGW, the HIV-1 version of this epitope.

**HXB2 Location** p24 (108–117)  
**Author Location** (C consensus)  
**Epitope** TSTLQEQIAW  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the T3 residue of TSTLQEQIAW are associated with the presence of the HLA presenting molecule in the host.
- TSTLQEQIAW is cross presented by both B\*5801 and B\*5703.

**HXB2 Location** p24 (108–117)

**Author Location** Gag (1513–)

**Epitope** TSTLQEIQGW

**Epitope name** TW10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801)

**Country** Australia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, HLA associated polymorphism

**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore *et al.*, Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- This HLA-B\*5801 HIV mutation association was only picked up using statistics that incorporate the phylogeny. The Thr at TstLQEIQGW at the third position is the HLA-correlated amino acid. A B57 association was also found for this cross-presented epitope.

**HXB2 Location** p24 (108–117)

**Author Location** p24

**Epitope** TSTLQEIQGW

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B\*5801)

**Assay type** Tetramer binding

**Keywords** binding affinity

**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently

expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.

- This epitope, TSTLQEQIGW (MHC Class I restriction, serotype Bw4Ile80) complexed with MHC B\*5801 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

**HXB2 Location** p24 (108–117)

**Author Location** (C consensus)

**Epitope** TSTLQEQIAW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (108–117)

**Author Location** Gag

**Epitope** TSTLQEQIGW

**Epitope name** TW10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27, B35, B57)

**Country** Australia, Canada, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** rate of progression, immunodominance, optimal epitope

**References** Streeck *et al.* 2007a

- To characterize HIV-1 proteome areas that are targeted in early, effective CTL responses, two cohorts were studied. Responses in early infection were against fewer epitopes and of lower magnitude than during chronic infection. While no region of the proteome was favored, Nef was the predominant target based on length of proteins. When based on the expression of protective versus nonprotective HLA I alleles, it was found that HLA-B27 and -57 possessing slow progressors to disease directed the majority of their responses to Gag in early infection, as opposed to those with HLA-B\*3501 or B\*3502, i.e. rapid progressors to AIDS, who had negligible responses to Gag. As compared with HLA-B57-/B27-subjects and HLA-B35 subjects, HLA-B57+/27+ subjects responded most to the p24 component of Gag. By using overlapping peptides within Gag p24, two were picked as being consistently targeted, and both contained previously described epitopes TW10 and KK10.

- TSTLQEQIGW, i.e. epitope TW10 is one of two immunodominant epitopes targeted during early infection in long term non-progressors to AIDS. After the acute phase of infection most subjects develop a variant, TSnLQEQIGW. Reversion to wild type is seen rapidly upon viral transmission to an HLA-B57- individual.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (233–252)

**Epitope** TSTLQEQIGW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population.
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was found in 3/6 INHIs.
- Epitope sequences were deduced from larger reactive peptides based on HLA binding motifs – XSXXXXXXXXW is a B57 binding motif, and CTL activity against TSTLQEQIGW has been found in two other B57 long-term non-progressors.

**HXB2 Location** p24 (108–117)

**Author Location** Gag (SF2)

**Epitope** TSTLQEQIGW

**Epitope name** TW10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** HAART, ART, acute/early infection

**References** Goulder *et al.* 2001a

- Dominant epitope in acute infection in patient PI004, who did not receive any antiviral therapy.
- 1-2 months post seroconversion, subject PI004 displayed a significant decrease in TW10 peptide recognition, followed by an increased CTL response against epitope SL9, SLYNTVATL and other epitopes.
- Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKR-WII, and FLKEKGGL were detectable at 5 months post-infection and beyond.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (108–117)

**Epitope** TSTLQEQIGW

**Epitope name** TST

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** HAART, ART, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses

and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.

- None of the 8 study subjects recognized this epitope but none were HLA B57+.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (108–117)

**Epitope** TSTLQEIQIGW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (108–117)

**Author Location** p24

**Epitope** TSTLQEIQIGW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2002

- Neisseria gonorrhoea cervicitis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhoea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

**HXB2 Location** p24 (108–117)

**Author Location** p24

**Epitope** TSTLQEIQIGW

**Epitope name** TST

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** p24 (108–117)

**Author Location** Gag (147–155)

**Epitope** TSTLQEIQIAW

**Epitope name** TW10

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** epitope processing, escape

**References** Draenert *et al.* 2004b

- 174 people who have C clade infections were studied – those who carried B57 have 2 positions in which their HIV Gag consensus is different than the C consensus. One mutation is within this epitope, TW10, at position 3, and is believed to be an anchor residue. The other is in the N-terminal flanking position of the epitope ISPRTLNAW and is thought to impact processing.

**HXB2 Location** p24 (108–117)

**Author Location** Gag (240–249)

**Epitope** TSTLQEIQIAW

**Epitope name** TW10

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** escape, viral fitness and reversion

**References** Leslie *et al.* 2004

- TSTLQEIQIAW (the consensus form in the C clade) responses dominate the immune response in HLA-B57 individuals, and this epitope is also recognized in HLA-B5801 individuals. TSnLQEIQIAW is shown to be an escape mutant correlated with HLA-B57 and HLA-B5801 alleles. The variant can be transmitted to HLA-B57/B5801 negative individuals, but reverts to wild-type in those. A second escape mutation within the epitope is, however, maintained after transmission; TSNLQEIQIGW is the most common form of the epitope in the B clade, and a G substitution to some other amino acid, often A, was frequently noted in B57+ individuals; transmission of these variants persist in the new host.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (108–117)

**Epitope** TSTLQEIQIGW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

**HXB2 Location** p24 (108–117)

**Author Location** (B consensus)

**Epitope** TSTLQEIQIGW

**Epitope name** TW10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** United Kingdom

- Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay
- Keywords** immunodominance, escape, characterizing CD8+ T cells
- References** Allen *et al.* 2004
- This study characterizes an escape mutation in a C-terminal flanking residue of the HLA-A3 gag p17 KK9 epitope that inhibits processing, and is embedded in the overlapping HLA-A3 RK9 epitope.
  - The immune response was tracked in subject AC-38. The acute immunodominant response was to the B57 TW10 epitope; this response declined following viral escape (tsNlqe-qigw) by day 64. The p17 KK9 and RK9 became immunodominant, but then declined as the escape mutation arose. TW10 is 1 of 3 other strong responses that persisted, along with 1 sub-dominant response.
- HXB2 Location** p24 (108–117)
- Author Location** Gag
- Epitope** TSTLQEIQIW
- Epitope name** TW10
- Subtype** B
- Immunogen** HIV-1 infection
- Species (MHC)** human (B57)
- Assay type** CD8 T-cell Elispot - IFN $\gamma$
- Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion
- References** Allen *et al.* 2005a
- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - Two escape mutations, at positions 3 (T242N) and 9 (G248A), were found in the most polymorphic residues in the epitope. Both were shared between clades B and C. Both were significantly more variable in persons expressing HLA-B57.
- HXB2 Location** p24 (108–117)
- Author Location** p24 (240–249)
- Epitope** TSTLQEIQIAW
- Epitope name** TW10
- Subtype** C
- Immunogen** HIV-1 infection
- Species (MHC)** human (B57)
- Country** Ethiopia
- Assay type** CD8 T-cell Elispot - IFN $\gamma$
- Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization
- References** Currier *et al.* 2005
- Epitope sequence variation and CD8 T-cell responses were analyzed in C subtype infected HLA-B57-positive individuals from Ethiopia. KF11 was the immunodominant response.
  - 9/10 B57 subjects had the T3N TSnLQEIQIAW substitution relative to the C consensus, while this form was found in only 2/9 B57- subjects, so it appears to be selected and an immune escape form ( $p=0.001$ ). Both forms of the TW10 epitope (TSTLQEIQIAW and TSnLQEIQIAW) were tested in 2 B57-positive subjects; neither responded. The authors suggest this
- may be due to the dominance of the TW10 response in acute infection, as the response may have been lost by the time of sampling.
- HXB2 Location** p24 (108–117)
- Author Location** Gag
- Epitope** TSTLQEIQIW
- Epitope name** TW10
- Immunogen** HIV-1 infection
- Species (MHC)** human (B57)
- Assay type** Other
- Keywords** rate of progression, escape
- References** Gao *et al.* 2005
- Three distinct HLA alleles known to alter the rate of AIDS progression were studied. B\*57-mediated protection occurs early in infection and the protective effect of this allele subsides after CD4 cell count drops. In contrast, B\*27 shows no protection against progression to CD4<200, but rather delays progression to an AIDS-defining illness after the CD4 counts have dropped. B\*35-mediated rapid progression to AIDS is probably a function of early decline in CD4 counts.
  - TW10 is typically the immunodominant B57 epitope. TW10 responses are rapid, and escape occurs but presumably with a fitness cost, because reversion occurs after the escape variant is transmitted to a B57- person. High CD4 counts may be maintained in individuals because of immune selection for a less fit form of the virus.
- HXB2 Location** p24 (108–117)
- Author Location** Gag (240–249)
- Epitope** TSTLQEIQIAW
- Subtype** C
- Immunogen** HIV-1 infection
- Species (MHC)** human (B57)
- Donor MHC** A\*3001, A\*66, B\*4201, B\*5802, Cw\*0602, Cw\*1701; A\*66, A\*68, B\*57, B\*5802, Cw\*0602, Cw\*0701
- Country** South Africa
- Assay type** CD8 T-cell Elispot - IFN $\gamma$
- Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection
- References** Pillay *et al.* 2005
- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
  - TSTLQEIQIAW is the C consensus form of the epitope and the autologous form in the mother was TSTLQEIQItW, and this was the form transmitted to her infant. The mother does not carry B57, and the B57 escape footprint was inherited paternally. By 33 weeks a new dominant form of the epitope had emerged in the infant, TSnLQEIQIAW, and the consensus form was also present in the infant.
- HXB2 Location** p24 (108–117)
- Author Location** p24
- Epitope** TSTLQEIQIW
- Epitope name** B57-TW10(p24)

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.
- This epitope, TSTLQEIQGW (TW10), elicits the HLA-B57 restricted response that is most dominant of the immune responses generated.

**HXB2 Location** p24 (108–117)

**Author Location**

**Epitope** TSTLQEIQGW

**Epitope name** B57-TW10

**Immunogen**

**Species (MHC)** (B57)

**Keywords** review, immunodominance, escape, vaccine antigen design

**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.

**HXB2 Location** p24 (108–117)

**Author Location** p24

**Epitope** TSTLQEIQGW

**Epitope name** TW10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Keywords** review, rate of progression, immunodominance, escape, acute/early infection, viral fitness and reversion

**References** Goulder & Watkins 2004

- This paper is a review of the role of CTL in HIV infection, and it uses the TW10 epitope as an example. HLA B\*57 and B\*5801 both can present this epitope, and are associated with successful containment of HIV infection. The early response to TW10 is immunodominant, and often followed by rapid escape due to the T->N substitution, tsNlqeqigw. Some long term survivors do not carry the escape form, possibly because the CTL response to this epitope is able to suppress viremia. Others do carry the N escape form, and presumably control viremia due to viral attenuation; in support of this the N rapidly back mutates to T in a new host, so there is likely to

be a high fitness cost. In contrast, the epitope sometimes contains a G-> A substitution at position 9, and the A can persist in a new host after transmission.

**HXB2 Location** p24 (108–117)

**Author Location** Gag

**Epitope** TSTLQEIQGW

**Epitope name** TW10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children did not respond to TSTLQEIQGW but showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- TW10 was found to be more frequently recognized by adults than by children. Among B57-positive subjects, TW10 was recognized by 10 out of 12 acutely infected adults, 11/22 chronically infected adults, and only 1/14 infected children. All 14 children carried mutations of this epitope, commonly T3N and G9A (TSnLQEIQaW), but the children were able to recognize the autologous variant. These mutations were rare in adults. One child carried T3N, Q5A, and G9A, and also recognized the autologous variant, TSnLaEQIaW.

**HXB2 Location** p24 (108–117)

**Author Location** p24

**Epitope** TSTLQEIQGW

**Epitope name** TW10

**Immunogen**

**Species (MHC)** (B\*5801, B57)

**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion

**References** Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (235–243)

**Epitope** TSTLQEIQGW

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B57, B58)



- Keywords** HIV exposed persistently seronegative (HEPS)
- References** Kaul *et al.* 2001a
- TSTLQEQIGW cross reacts with both A and B clades.
  - ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- HXB2 Location** p24 (108–117)
- Author Location** p24 (108–117)
- Epitope** TSTLQEQIGW
- Immunogen** HIV-1 infection
- Species (MHC)** human (B57, B58)
- Donor MHC** A1, A26, B35, B57, Cw\*0601, Cw4; A1, A30, B42, B52, Cw17, Cw7; A\*0201, A1, B44, B57, Cw5, Cw6
- Assay type** CD8 T-cell Elispot - IFN $\gamma$
- Keywords** binding affinity, acute/early infection, early-expressed proteins, cross-presentation by different HLA
- References** Cao *et al.* 2003
- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
  - This epitope was recognized in three of the acutely infected individuals and was presented by both HLA-B57 and B58.
  - More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.
  - All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- HXB2 Location** p24 (108–117)
- Author Location** Gag (240–249)
- Epitope** TSTLQEQIGW
- Epitope name** gag 240-9
- Immunogen** HIV-1 infection, HIV-2 infection
- Species (MHC)** human (B57, B58)
- Country** Gambia
- Assay type** Intracellular cytokine staining
- Keywords** escape, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, HIV-2
- References** Lopes *et al.* 2003
- CD8+ T cells from HIV-2 infected patients had more polyclonal TCR responses than HIV-1 infected patients, who tended to have oligoclonal responses. This results in limited plasticity of T cell responses to amino acid substitutions within epitopes in HIV-1 infections. HIV-2-specific CD8+ T-cells showed a more diverse TCR usage associated with enhanced CD8 expansion and IFN-gamma production on cross-recognition of variant epitopes.
  - This peptide was recognized by a CD8+ T-cell clonotype with Vbeta5.1 usage in one HIV-1 infected patient, and all HIV-1 patients had narrow TCR usage, while HIV-2 patients used multiple TCR Vbeta chains. The HIV-2 variant of this peptide is: tstVEeqiQw. 5/6 HIV-2 infected individuals could recognize both the HIV-1 and HIV-2 peptides, while 0/5 HIV-1 infected patients that could react with the HIV-1 peptide could also react with the HIV-2 peptide.
- HXB2 Location** p24 (108–117)
- Author Location** p24
- Epitope** TSTLQEQIGW
- Subtype** B, C
- Immunogen** HIV-1 infection
- Species (MHC)** human (B57, B58, B63)
- Assay type** CD8 T-cell Elispot - IFN $\gamma$
- Keywords** rate of progression, cross-presentation by different HLA, optimal epitope
- References** Frahm *et al.* 2005
- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
  - This epitope was recognized by 30% of B63-positive subjects and 22% of B57/58-positive subjects.
- HXB2 Location** p24 (108–117)
- Author Location** p24 (241–250)
- Epitope** TSTVEEQIHW
- Subtype** HIV-2
- Immunogen** HIV-2 infection
- Species (MHC)** human (B58)
- Country** Gambia
- Keywords** HIV-2
- References** Bertoletti 1998
- HIV-2 epitope defined from an infection in Gambia, Bertoletti, pers. comm.
  - All HIV-2 sequences from the database are TSTVEEQIQW in this region, not TSTVEEQW as in the paper.
- HXB2 Location** p24 (108–117)
- Author Location** p24
- Epitope** TSTLQEQIGW
- Immunogen** HIV-1 exposed seronegative
- Species (MHC)** human (B58)
- References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: TSTVEEQIQW, CTL are cross-reactive, Bertoletti *et al.* [1998]

**HXB2 Location** p24 (108–117)

**Author Location** p24 (240–249)

**Epitope** TSTLQEQIGW

**Subtype** HIV-2

**Immunogen** HIV-2 infection

**Species (MHC)** human (B58)

**Keywords** subtype comparisons, rate of progression, immunodominance, HIV-2

**References** Bertoletti *et al.* 1998

- CTL responses in HLA-B\*5801 positive HIV-2 infected individuals have a dominant response to Gag and tolerate extensive substitution, thus HLA-B\*5801+ individuals may have an enhanced potential for cross-protection between HIV-1 and HIV-2.
- This can be an immunodominant epitope in HLA-B57 and B\*5801 infected individuals, and is associated with long-term non-progression Goulder *et al.* [1996b]
- HIV-2 sequence: HIV-2 ROD has the epitope sequence TSTVEEQIQW, and the CTL from a person infected with HIV-2 was cross-reactive with HIV-1 epitopes.
- The epitope is TSTLQEQIGW in HIV-1 B clade, and TSTVEEQIQW in HIV-2 ROD.
- HLA B\*5801 and B35 may preferentially select HIV-1 and HIV-2 cross-reactive epitopes.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (240–249 SF2)

**Epitope** TSTLQEQIGW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B58)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B58+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 1/1 group 2, and 0/0 group 3.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (108–117)

**Epitope** TSTLQEQIGW

**Epitope name** TW10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B58)

**Keywords** acute/early infection

**References** Goulder *et al.* 2001c

- Responses to this dominant A3-restricted Gag epitope are present during the time of decreasing viral load in acute infection.
- Mutations in this epitope were observed in autologous clones of subjects who were B58-positive with a higher frequency than those who were B58-negative (P = 0.02)
- These mutations are being sexually transmitted in adult infections.

**HXB2 Location** p24 (108–117)

**Author Location** p24 (108–117)

**Epitope** TSTLQEQIGW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate reversion rates for this epitope, TSTLQEQIGW, in 3 different subjects were found to be 0.016, 0, and 0.005/day with SEs of 0.007, 0, and 0.001 respectively.
- Gag p24 T110N confers escape in subjects expressing HLA-B57 and HLA-B5801. On transmission from an HLA-B57+ donor to an B57/B5801- recipient, the mutation rapidly reverted to wild type (a=0.016/day). Gag p24 G116A confers escape in subjects expressing B57 and B5801. On transmission from an HLA-B57+ donor to an B57/B5801- recipient, the mutation did not revert to wild type over the 8-year observation period, suggesting that the mutation was neutral (a=0/day). The escape variant in Gag p24 T110N was studied in a further HLA-B57+ to HLA-B57/B5801- transmission pair where it reverted to wild type (a=0.005/day).

**HXB2 Location** p24 (108–117)

**Author Location**

**Epitope** TSTLQRQIGW

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls (ML1250).

**HXB2 Location** p24 (108–117)

**Author Location** Gag (B57)

**Epitope** TSNLQEQIGW

**Epitope name** TW10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Characteristic changes in B57 epitopes in B57+ people were mapped: TSNLQEQIGW often has one or both of the substitutions: tsNlqeqygw, tstlqeqy[A/G]w.

**HXB2 Location** p24 (108–117)

**Author Location**

**Epitope** TSTLQEQIGW

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0101, A\*2902; B\*1501, B\*5701

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.

- TSTLQEQIGW was recognized by a placebo patient after infection.

**HXB2 Location** p24 (108–118)

**Author Location** p24 (240–249 LAI)

**Epitope** TSTLQEQIGW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57, B\*5801)

**Keywords** rate of progression

**References** Goulder *et al.* 1996b

- Response to this epitope was found in 4 slow progressing HLA-B\*57 individuals, in 2 it was dominant or very strong.
- For one donor (from Zimbabwe) this was defined as the optimal peptide.
- This epitope can be presented in the context of the closely related HLA molecules B\*5801 and B\*57.

**HXB2 Location** p24 (108–118)

**Author Location**

**Epitope** TSTLQEQIGW

**Epitope name** Gag-TF11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 2/5 (40%) recognized this epitope.

**HXB2 Location** p24 (109–117)

**Author Location** Gag (241–249 LAI)

**Epitope** STLQEQIGW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701, B\*5801)

**Keywords** rate of progression

**References** Klein *et al.* 1998

- B57 has been associated with long-term non-progression in the Amsterdam cohort.
- The most pronounced CTL responses in HLA B\*5701 LTS were to RT and Gag.

**HXB2 Location** p24 (109–117)

**Author Location**

**Epitope** STLQEQIGW

**Epitope name** Gag-SW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 1/5 (20%) recognized this epitope.
- Among HIV+ individuals who carried HLA B58, 1/4 (25%) recognized this epitope.

**HXB2 Location** p24 (109–117)

**Author Location** p24

**Epitope** STLQEQIGW

**Subtype** B, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B58)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The epitope sequence in this person had a single G8A change, STLQEQIaW.

**HXB2 Location** p24 (109–118)

**Author Location** p24 (110–118)

**Epitope** STLQEQIGWM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, STLQEQIGWM, was detected within overlapping peptides SDIAGTTSTLQEQIGWM and WMTNPPPIPVEIYKRWI.

**HXB2 Location** p24 (110–118)

**Author Location** Gag (242–)

**Epitope** TLQEQIGWM

**Epitope name** Gag242

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* p24 Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder that did not induce CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

**HXB2 Location** p24 (110–118)

**Author Location** Gag (242–250 Henan isolate)

**Epitope** NLQEQIGWM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- NLQEQIGWM was among 5 mostly recognized epitopes (69%).

**HXB2 Location** p24 (110–119)

**Author Location** Gag (Henan isolate)

**Epitope** NLQEQIGWMT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p24 (117–126)

**Author Location** p24 (Henan isolate)

**Epitope** WMTNPPPIPV

**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006
- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
  - WMTNNPIPVPV was among 5 mostly recognized epitopes (69%).
- HXB2 Location** p24 (117–134)  
**Author Location** p24  
**Epitope** WMTNNPIPVPVGEIYKRWI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B53, B8)  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004
- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
  - Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
  - In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
  - This frequently targeted overlapping peptide, WMTNNPIPVPVGEIYKRWI, was differentially targeted across ethnic groups and had an overall frequency of recognition of 16% - 25.4% AA, 23.1% C, 2.3% H, 9.5% WI (P value = 0.0035). This peptide is included in a 41 aa Gag-p24 highly reactive region to be used for vaccine design.
- HXB2 Location** p24 (117–134)  
**Author Location** Gag (251–268)  
**Epitope** MYRQQNPVPVGNIRRWI  
**Subtype** HIV-2  
**Immunogen** HIV-2 infection  
**Species (MHC)** human  
**Country** Guinea-Bissau  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** rate of progression, optimal epitope, HIV-2  
**References** Leligdowicz *et al.* 2007
- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.
  - This peptide, MYRQQNPVPVGNIRRWI, was recognized by 11 out of 65 subjects. It is found in the 149 amino-acid long HIV-2 proteome region of Gag 175-323.
- HXB2 Location** p24 (118–126)  
**Author Location** p24 (118–126)  
**Epitope** MTNNPIPVPV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007
- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
  - This epitope, HPVHAGPIAPGQMREPR, was detected within overlapping peptideS LHPVHAGPIAPGQMREPR, LKETINEEAAEWDR LHPV and AAEWDR LHPVHAGPIA.
- HXB2 Location** p24 (118–126)  
**Author Location** Gag  
**Epitope** MTSNPIPVPV

**Epitope name** Gag 271**Subtype** M**Immunogen** vaccine, in vitro stimulation or selection  
*Vector/Type:* DNA, peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)**Species (MHC)** human, mouse (A\*0201)**Assay type** Cytokine production, T-cell Elispot**Keywords** subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization**References** McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A\*0201 and A\*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- MTSNPPIPV form is most common in subtype C while MTnNPPIPV form is mostly found in subtype B.
- A total of 14 variant forms of Gag 271 were identified. Immunization with MTSNPPIPV form induced CTLs recognizing 11 of the variant forms while MTnNPPIPV form induced CTLs recognizing only 3 of the epitope variants.

**HXB2 Location** p24 (118–126)**Author Location** p24 (118–126)**Epitope** MTNPPPIPV**Epitope name** MV9**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Donor MHC** A\*02, A\*23, B\*07, B\*51, Cw\*15**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- The mother was A02- and carried a variant form of the epitope, MThNPPIPV, which she passed to her A02+ child. This form persisted in her child for 12 months.

**HXB2 Location** p24 (118–126)**Author Location** Gag (282–290)**Epitope** MTNPPPIPV**Immunogen** HIV-1 infection**Species (MHC)** human (A2 supertype)**Keywords** supertype, rate of progression**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertype alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

**HXB2 Location** p24 (121–135)**Author Location** p24 (253–267)**Epitope** NPPIPVGGEIYKRWII**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**References** Gotch *et al.* 1990

- High frequency of memory and effector Gag-specific CTL.

**HXB2 Location** p24 (121–135)**Author Location** p24 (255–274 SF2)**Epitope** NPPIPVGGEIYKRWII**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Keywords** review, immunodominance, escape**References** Goulder *et al.* 1997a; Phillips *et al.* 1991

- Longitudinal study of CTL escape mutants in people with the appropriate HLA types – little variation was observed in the immunodominant B27 epitope, relative to B8 epitopes, which varied over time.
- Goulder *et al.* [1997a] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA B27 patients.

**HXB2 Location** p24 (121–135)**Author Location** p24 (121–135)**Epitope** NPPIPVGGEIYKRWII**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (121–135)**Author Location** p24 (121–135 HXB2)**Epitope** NPPIPVGGEIYKRWII**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** T-cell Elispot**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STL.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p24 (121–140)

**Author Location** p24 (253–272)

**Epitope** NPPIPVGEIYKRWIILGLNK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** p24 (121–140)

**Author Location** p24 (253–272 SF2)

**Epitope** NPPIPVGEIYKRWIILGLNK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- Two of these 12 had CTL response to this peptide.
- The responding subjects were HLA-A2, A3, B8, B62, and HLA-A1, B8, B18.

**HXB2 Location** p24 (121–140)

**Author Location** p24 (253–272 SF2)

**Epitope** NPPIPGEIKRWIILGNIK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** p24 (121–140)

**Author Location** p24 (255–274 SF2)

**Epitope** NPPIPVGEIYKRWIILGLNK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** van Baalen *et al.* 1993

- Gag CTL epitope precursor frequencies were estimated and peptide mapping was performed.

**HXB2 Location** p24 (121–142)

**Author Location** p24 (253–274 BH10)

**Epitope** NPPIPVGEIYKRWIILGLNKIV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

**HXB2 Location** p24 (121–152)

**Author Location** Gag

**Epitope** NPPIPVGEIYKRWIILGLNKIVRMYSPTSILD

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* lipopeptide *HIV component:*

Gag

**Species (MHC)** human (A\*0201)

**References** Seth *et al.* 2000

- Immunization of 2/4 HIV seropositive HLA selected individuals with a 32 amino acid Gag lipopeptide that contains CTL epitopes restricted by HLA A33, B8, B27, B35, and Bw62 gave a transient increase in peptide-specific bulk CTL response, but they did not decrease plasma viral load.
- Placebo and HLA mis-matched controls showed no change in CTL.
- The responders carried HLA Bw62 and B35 – the two HLA-matched that did not respond carried B35 and B8.

**HXB2 Location** p24 (121–152)

**Author Location** Gag (183–214 LAI)

**Epitope** NPPIPVGEIYKRWIILGLNKIVRMYSPTSILD

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide

**Species (MHC)** human

**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 9/10 reacted to this peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in four vaccinees.
- All of the 12 tested had an IgG response to this peptide.

**HXB2 Location** p24 (122–130)

**Author Location** (C consensus)

**Epitope** PPIPVGDIY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the D7 residue of PPIPVGDIY are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** p24 (122–130)

**Author Location** (C consensus)

**Epitope** PPVPGDIY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- PPVPGDIY is an optimal epitope.

**HXB2 Location** p24 (122–130)

**Author Location** p24 (260–268 LAI)

**Epitope** PPIPVGDIY

**Subtype** B

**Immunogen** HIV-1 or HIV-2 infection

**Species (MHC)** human (B\*3501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*3501 epitope. Variant nPvPVGDIY also noted.

**HXB2 Location** p24 (122–130)

**Author Location** p24 (245–253)

**Epitope** NPVPVGNIY

**Subtype** HIV-2

**Immunogen** HIV-1 or HIV-2 infection

**Species (MHC)** human (B\*3501)

**Country** Gambia

**Keywords** HIV exposed persistently seronegative (HEPS), HIV-2

**References** Rowland-Jones *et al.* 1995

- HIV-2 epitope NPVPVGNIY was recognized by CTL from HIV-1-infected and HIV-2-infected B35+ subjects.

**HXB2 Location** p24 (122–130)

**Author Location** Gag

**Epitope** PPIPVGDIY

**Epitope name** PY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501, B\*3502)

**Country** Australia, Canada, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** rate of progression, immunodominance, optimal epitope

**References** Streeck *et al.* 2007a

- To characterize HIV-1 proteome areas that are targeted in early, effective CTL responses, two cohorts were studied. Responses in early infection were against fewer epitopes and of lower magnitude than during chronic infection. While no region of the proteome was favored, Nef was the predominant target based on length of proteins. When based on the expression of protective versus nonprotective HLA I alleles, it was found that HLA-B27 and -57 possessing slow progressors to disease directed the majority of their responses to Gag in early infection, as opposed to those with HLA-B\*3501 or B\*3502, i.e. rapid progressors to AIDS, who had negligible responses to Gag. As compared with HLA-B57-/B27-subjects and HLA-B35 subjects, HLA-B57+/27+ subjects responded most to the p24 component of Gag. By using overlapping peptides within Gag p24, two were picked as being consistently targeted, and both contained previously described epitopes TW10 and KK10.
- PPIPVGDIY, i.e. epitope PY9 was targeted in 10% of rapid progressors to disease.

**HXB2 Location** p24 (122–130)

**Author Location** p24 (260–268 LAI)

**Epitope** PPIPVGDIY

**Subtype** B

**Immunogen** HIV-1 or HIV-2 infection

**Species (MHC)** human (B35)

**Keywords** HIV exposed persistently seronegative (HEPS), HIV-2

**References** Rowland-Jones *et al.* 1995

- Defined as minimal peptide by titration curve, PPIPVGDIY; HIV-2 form NPVPVGNIY is also recognized.

**HXB2 Location** p24 (122–130)

**Author Location** p24 (260–268 LAI)

**Epitope** PPIPVGDIY

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (B35)

**References** Lalvani *et al.* 1997

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers.
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors.

**HXB2 Location** p24 (122–130)

**Author Location** p24 (260–268 LAI)

**Epitope** PPIPVGDIY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** review

**References** McMichael & Walker 1994



- Review of HIV CTL epitopes.

**HXB2 Location** p24 (122–130)

**Author Location** p24 (subtype B)

**Epitope** PPIPVGIEY

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B35)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope, PPIPVGDIY, was preferentially recognized by CTL.

**HXB2 Location** p24 (122–130)

**Author Location**

**Epitope** PPIPVGIEY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** acute/early infection

**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers—high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWILGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGIEY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** p24 (122–130)

**Author Location** p24

**Epitope** PPIPVGDIY

**Immunogen**

**Species (MHC)** human (B35)

**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 version of this epitope is not conserved: NPVPVGNIIY, but the CTLs are cross-reactive – one of five B35 CTL epitopes that are cross-reactive, see also Rowland-Jones *et al.* [1995]

**HXB2 Location** p24 (122–130)

**Author Location** p24 (260–268)

**Epitope** PPIPVGDIY

**Epitope name** PPI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** HAART, ART, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- One of two HLA B35+ among the eight study subjects recognized this epitope.
- Patient SC15 (HLA A1/68, B8/35, Bw4/6, Cw4/0704) was given acute and sustained therapy and recognized epitopes PPIPVGDIY and VPLRPMTY during 331 days of HAART treatment.

**HXB2 Location** p24 (122–130)

**Author Location** p24 (122–130)

**Epitope** PPIPVGDIY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (122–130)

**Author Location** p24 (254–262 SF2)

**Epitope** PPIPVGDIY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic

infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.

- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 0/2 group 2, and 1/1 group 3.

**HXB2 Location** p24 (122–130)

**Author Location** p24 (260–268)

**Epitope** PPIPVGDIY

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B35)

**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B35 women, 1/3 HEPS and 3/4 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in the 1/3 HEPS case and in the all 3/4 responsive HIV-1 infected women.
- Subject ML 857 shifted from a A\*6802 DTVLEDINL and B35 (H/N)PDIVIQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMY response post-seroconversion.

**HXB2 Location** p24 (122–130)

**Author Location**

**Epitope** PPIPVGDIY

**Epitope name** Gag-PY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 2/21 (10%) recognized this epitope.
- Among HIV+ individuals who carried HLA B\*5301, 0/11 (0%) recognized this epitope.

**HXB2 Location** p24 (122–130)

**Author Location** p24

**Epitope** PPIPVGDIY

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human (B35)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polypeptide string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polypeptide string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  ELISPOT assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polypeptide region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polypeptide string Wee *et al.* [2002].

**HXB2 Location** p24 (122–130)

**Author Location** p24 (260–268)

**Epitope** PPIPVGDIY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** United States

**Assay type** CD8 T-cell ELISPOT - IFN $\gamma$ , CD8 T-cell ELISPOT granzyme B

**Keywords** characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN- $\gamma$  and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30–40% of the CD8 cell pool. One of these (Tc1b) secretes IFN- $\gamma$  only, and the other one (Tc1c) secretes GzB only.
- None of three patients responded to this peptide with GzB producing cells and one of the patients responded with IFN- $\gamma$  producing cells.

**HXB2 Location** p24 (122–130)

**Author Location** Gag

**Epitope** PPIPVGDIY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** Netherlands

**Assay type** CD8 T-cell ELISPOT - IFN $\gamma$

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- No one, 0/3 HLA B35+ infection-resistant men, and 0/5 pre-seroconversion men who went on to become infected, reacted to this epitope.

**HXB2 Location** p24 (122–130)

**Author Location** p24 (122–130)

**Epitope** PPIPVGDIY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 4/9 patients recognized this epitope.

**HXB2 Location** p24 (122–130)

**Author Location** (C consensus)

**Epitope** PPVPVGDIIY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (122–130)

**Author Location** p24

**Epitope** PPIPVGIEIY

**Subtype** B, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35, B53)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence in this person matched the known epitope. In another D subtype infected individual, it was predicted to be a B53 epitope based on HLA typing of the individual and motifs within the reactive peptide.

**HXB2 Location** p24 (122–130)

**Author Location** Gag (254–262)

**Epitope** PPIPVGIEIY

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (B7 supertype)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** p24 (122–130)

**Author Location** p24

**Epitope** PPIPVGDIH

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.

- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML887.

**HXB2 Location** p24 (122–130)

**Author Location**

**Epitope** PPIPVGDIY

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN  
*HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A2A2; B35, B62

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85–86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** p24 (124–138)

**Author Location** p24 (256–270 LAI)

**Epitope** IPVGEIYKRWIILGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Buseyne *et al.* 1993b

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people.

**HXB2 Location** p24 (124–138)

**Author Location** Gag (256–270 LAI)

**Epitope** IPVGEIYKRWIILGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Two children, EM16 (CDC P2A+D2) and EM18 (CDC P2A), had a CTL response to this epitope, and it was shown to be presented by B8 in EM18.

**HXB2 Location** p24 (125–135)

**Author Location** Gag (264–274)

**Epitope** PVGDIYKRWII

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p24 (125–142)

**Author Location** p24

**Epitope** PVGEIYKRWIILGLNKIV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27, B8)

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J.Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.

- This frequently targeted overlapping peptide, PVGEIYKRWI-ILGLNKIV, was differentially targeted across ethnic groups and had an overall frequency of recognition of 22% - 30.5% AA, 42.3% C, 9.1% H, 4.8% WI (P value = 0.001). This peptide is included in a 41 aa Gag-p24 highly reactive region to be used for vaccine design.

**HXB2 Location** p24 (125–142)

**Author Location** Gag (259–276)

**Epitope** PVGNIYRRWIQIGLQKCV

**Subtype** HIV-2

**Immunogen** HIV-2 infection

**Species (MHC)** human

**Country** Guinea-Bissau

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** rate of progression, optimal epitope, HIV-2

**References** Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.
- This peptide, PVGNIYRRWIQIGLQKCV, was recognized by 9 out of 65 subjects. It is found in the 149 amino-acid long HIV-2 proteome region of Gag 175-323.

**HXB2 Location** p24 (126–140)

**Author Location** p24 (126–140 HXB2)

**Epitope** VGEIYKRWIIGLNK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.

- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.

- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p24 (127–135)

**Author Location** p24 (259–267 SF2)

**Epitope** GDIYKRWII

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**References** McAdam *et al.* 1998

- GDIYKRWII specific CTL clone also recognized GEIYKRWII.

**HXB2 Location** p24 (127–135)

**Author Location** p24 (127–135)

**Epitope** GEIYKRWII

**Epitope name** GEI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells

**References** Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B8-GEI, that is associated with rapid progression to AIDS, and its natural as well as alanine-substituted variants are either not cross-recognized or show high inter-patient variability in cross-recognition. At lower peptide concentrations, efficiency of variant cross-recognition was reduced, even while interepitopic differences in variant cross-recognition efficiency were maintained. CTLs responding to this epitope expressed the same predominant TCR Vbeta family.

**HXB2 Location** p24 (127–135)

**Author Location** p24 (261–269)

**Epitope** GEIYKRWII

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Sutton *et al.* 1993

- Predicted epitope based on B8-binding motifs, from larger peptide NPPIPVGEIYKRWII.

**HXB2 Location** p24 (127–135)**Author Location** p24 (259–267)**Epitope** GEIYKRWII**Immunogen** in vitro stimulation or selection**Species (MHC)** human (B8)**Keywords** dendritic cells**References** Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYK-TLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

**HXB2 Location** p24 (127–135)**Author Location** p24 (259–267 LAI)**Epitope** GEIYKRWII**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**References** Klenerman *et al.* 1994

- Naturally occurring variant GDIYKRWII may act as antagonist.

**HXB2 Location** p24 (127–135)**Author Location** p24 (259–267)**Epitope** GEIYKRWII**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Keywords** immunodominance**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the HLA A2+ was HLA A\*0201, A31, B8, B51 and responded to this epitope as well as seven others.

**HXB2 Location** p24 (127–135)**Author Location** p24 (259–267)**Epitope** GEIYKRWII**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Keywords** dynamics, escape**References** Nowak *et al.* 1995

- Longitudinal study of CTL response and study of immune escape – GDIYKRWII could also stimulate CTL, reactivity fluctuated.

**HXB2 Location** p24 (127–135)**Author Location** p24 (259–267)**Epitope** GEIYKRWII**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**References** McAdam *et al.* 1995

- Equivalent sequence GDIYKRWII also recognized by CTL from some donors.

**HXB2 Location** p24 (127–135)**Author Location** p24 (259–267)**Epitope** GEIYKRWII**Epitope name** GEI**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, escape, acute/early infection**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- Six of the 7/8 study subjects that were HLA B8 recognized this epitope.
- Patient SC2 (HLA A1, B7/8, Cw0701/0702, DR4/53, DQ7) had CTL responsiveness against epitopes FLKEKGGL, GPKVKQWPL, and GEIYKRWII peptides – FLKEKGGL tetramer staining steadily declined and at day 1340 the FLKEKGGL stained cells were no longer detected and the escape mutant FLKENGGI was found in 8/10 clones.
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDWIYHTQGYFPDWQNY, and GEIYKRWII and all responses declined during therapy initiated at day 390 but were restored when therapy become intermittent.
- Patient SC19 (HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSH-FLK, and FNCGGEFFY that declined during therapy initiated at day 197.
- Patient SC10 (HLA A1/3, B8/35, DR1/8, DQ 4/5) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL and a response to GEIYKRWII through day 1088.
- Patient SC12 (HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKCKYKLLK – GEIYKRWII and GGKCKYKLLK responses were stimulated by a brief period off therapy.
- Patient SC11 (HLA A1, B8, Cw0201, DR3/11, DR52, DQ2/7) started therapy early, remained on therapy for 40 days, then reinitiated HAART at day 640 had a CTL response to FLKEKGGL, GPKVKQWPL, and GEIYKRWII throughout and received a benefit from the early limited course therapy.

- HXB2 Location** p24 (127–135)  
**Author Location** p24 (259–267 SF2)  
**Epitope** GEIYKRWII  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b
- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
  - The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
  - Previously described and newly defined optimal epitopes were tested for CTL response.
  - Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 2/3 group 1, 2/3 group 2, and 2/2 group 3.

- HXB2 Location** p24 (127–135)  
**Author Location** p24  
**Epitope** GEIYKRWII  
**Epitope name** GEI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** HAART, ART, supervised treatment interruptions (STI)  
**References** Oxenius *et al.* 2002b
- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
  - STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

- HXB2 Location** p24 (127–135)  
**Author Location** p24  
**Epitope** GEIYKRWII  
**Subtype** A, B, C, D  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag  
**Species (MHC)** human (B8)  
**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance  
**References** Hanke & McMichael 2000; Wee *et al.* 2002
- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to

- have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

- HXB2 Location** p24 (127–135)  
**Author Location** Gag (259–267)  
**Epitope** GEIYKRWII  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21  
**Species (MHC)** human (B8)  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization  
**References** Gahéry-Ségard *et al.* 2003
- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

- HXB2 Location** p24 (127–135)  
**Author Location** p24 (259–267)  
**Epitope** GEIYKRWII  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B  
**Keywords** Th1, characterizing CD8+ T cells  
**References** Kleen *et al.* 2004
- Only 20% of CD8+ T-cells produce IFN- $\gamma$  and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN- $\gamma$  only, and the other one (Tc1c) secretes GzB only.
  - None of three patients responded to this peptide with GzB producing cells and one of the patients responded with IFN- $\gamma$  producing cells.

- HXB2 Location** p24 (127–135)  
**Author Location** p24

**Epitope** GEIYKRWII**Subtype** B, D**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Donor MHC** A1A1, B55, B8, Cw3, Cw7**Country** Democratic Republic of the Congo**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence matched the peptide.

**HXB2 Location** p24 (127–135)**Author Location** Gag (259–267 BRU)**Epitope** GEIYKRWII**Subtype** B, CRF02\_AG**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Country** Cote D'Ivoire**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 1/9 CRF02\_AG-infected Ivoirians, and 2/9 B-infected French subjects.

**HXB2 Location** p24 (127–136)**Author Location****Epitope** GEIYKRWIIL**Epitope name** Gag-GL10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*0801)**Donor MHC** A\*0101, A\*0301, B\*0801, B\*5802, Cw\*0602, Cw\*0701**Assay type** Chromium-release assay**Keywords** HAART, ART**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.

- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Among HIV+ individuals who carried HLA B08, 3/6 (50%) recognized this epitope.

**HXB2 Location** p24 (128–135)**Author Location** p24 (128–135)**Epitope** EIYKRWII**Epitope name** EI8**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*08)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** binding affinity, subtype comparisons, acute/early infection**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this epitope, EI8 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen to both A- and C-clade variants. Anchor residues are at positions 4 and 5; while both A- and C- variants contain a change at position 1 to dIYKRWII.

**HXB2 Location** p24 (128–135)**Author Location****Epitope** EIYKRWII**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*08)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** characterizing CD8+ T cells**References** Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.



- B\*08-restricted epitope EIYKRWII does not correlate with any particular CTL maturation phenotype.

**HXB2 Location** p24 (128–135)  
**Author Location** p24 (260–267 LAI)  
**Epitope** EIYKRWII  
**Subtype** B

**Immunogen**  
**Species (MHC)** human (B\*0801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0801 epitope.

**HXB2 Location** p24 (128–135)  
**Author Location** (C consensus)  
**Epitope** DIYKRWII  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (128–135)  
**Author Location** (C consensus)  
**Epitope** DIYKRWII  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- DIYKRWII is an optimal epitope.

**HXB2 Location** p24 (128–135)  
**Author Location** p24  
**Epitope** DIYKRWII  
**Epitope name** DI8  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)

**Country** South Africa

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization

**Keywords** rate of progression

**References** Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naïve patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B\*0801 DI8 was used to test 27 patients and gave a median ex vivo tetramer frequency of 0.55.

**HXB2 Location** p24 (128–135)  
**Author Location** p24

**Epitope** DIYKRWII  
**Immunogen** peptide-HLA interaction  
**Species (MHC)** human (B\*0801)  
**Assay type** Tetramer binding  
**Keywords** binding affinity  
**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, DIYKRWII (MHC Class I restriction, serotype Bw6) complexed with MHC B\*0801 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

**HXB2 Location** p24 (128–135)  
**Author Location**

**Epitope** DIYKRWII  
**Epitope name** DI8  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Country** South Africa  
**Assay type** proliferation, Tetramer binding, Intracellular cytokine staining  
**References** Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

**HXB2 Location** p24 (128–135)  
**Author Location** p24 (260–267 LAI)  
**Epitope** EIYKRWII  
**Subtype** B

**Immunogen**  
**Species (MHC)** human (B8)  
**References** Goulder *et al.* 1997g

- Defined in a study of the B8 binding motif.

**HXB2 Location** p24 (128–135)

**Author Location** p24 (SF2)

**Epitope** EIYKRWII

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in an HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71–85), SALSEGATPQDLNLTMLNTVG (p24 41–60), and WEKIRL-RPGGKKKYK (p17 16–30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20–36), ELRSLYNTVATLYCV (p17Gag 74–88), SALSEGATPQDLNLTMLNTVG (p24 41–60), FRDYVDRFFKTLRAEQA (p24 161–177), and SILDIKQGKEPFRDY (p24 149–164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (128–135)

**Author Location** p24 (C consensus)

**Epitope** DIYKRWII

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in an HIV+ South African – this epitope did not fall within the five most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71–85), SALSEGATPQDLNLTMLNTVG (p24 41–60), and WEKIRL-RPGGKKKYK (p17 16–30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20–36), ELRSLYNTVATLYCV (p17Gag 74–88), SALSEGATPQDLNLTMLNTVG (p24 41–60), FRDYVDRFFKTLRAEQA (p24 161–177), and SILDIKQGKEPFRDY (p24 149–164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (128–135)

**Author Location** p24 (SF2)

**Epitope** EIYKRWII

**Epitope name** EI8

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Goulder *et al.* 2001a

- This peptide elicited a weak CTL response during acute HIV-1 infection in patient PI004.
- Three CTL responses to epitopes, TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIMPF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond.

**HXB2 Location** p24 (128–135)

**Author Location** p24

**Epitope** EIYKRWII

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** rate of progression

**References** Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.
- 4/13 patients that reacted with EIYKRWII displayed epitope mutations in a minority of sequences, which did not correlate with disease progression or viral load – these mutations were: Patient 156 (KIYKRWMI), Patient 36 (EIYKRRII), Patient 656 (KIYKRWII, EIYERWMI), and Patient 159 (EIYKRWVI).
- Stimulation with HLA-B8 p24 and Nef epitopes significantly increased Nef-specific T-cell numbers in 2 patients (748 and 1113)
- There were more functional IFN-gamma producing Nef-specific T-cells within the T-cell population than there were active p24 Gag-specific T-cells.

**HXB2 Location** p24 (128–135)

**Author Location** p24 (259–267)

**Epitope** DIYKRWII

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$

**HXB2 Location** p24 (128–135)

**Author Location** p24 (128–135)

**Epitope** EIYKRWII

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

**HXB2 Location** p24 (128–135)

**Author Location** Gag

**Epitope** EIYKRWII

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Goulder *et al.* 2000b

- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA])
- HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection.

**HXB2 Location** p24 (128–135)**Author Location** p24**Epitope** DIYKRWII**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Donor MHC** A11, A2, B60, B8, Bw6**Keywords** HAART, ART**References** Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful antiviral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2–4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

**HXB2 Location** p24 (128–135)**Author Location** Gag (260–267 IIIIB)**Epitope** EIYKRWII**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Assay type** Chromium-release assay**References** Kurane *et al.* 2003

- Three CD8+ CTL cell clones were derived from 2 HIV-1 positive asymptomatic patients, and their epitope specificities and HLA presenting proteins were defined.

**HXB2 Location** p24 (128–135)**Author Location** Gag (B con)**Epitope** EIYKRWII**Epitope name** E18**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** variant cross-recognition or cross-neutralization**References** Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2–39) epitopic regions were targeted in an average of 6 proteins (range, 1–8). HAART resulted in decrease in antigen and reduction in gamma IFN Elispot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that

persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.

- 3 subjects recognized this epitope with intermediate functional avidity. Autologous sequence revealed one substitution, Diyrkwil, in 1 of the 3; this version of the epitope also had intermediate functional avidity with the donor's cells.

**HXB2 Location** p24 (128–135)**Author Location** Gag**Epitope** EIYKRWII**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Country** Netherlands**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** HIV exposed persistently seronegative (HEPS)**References** Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- 3/9 HLA B8+ infection-resistant men, compared to 1/3 pre-seroconversion men who went on to become infected, reacted to this epitope.

**HXB2 Location** p24 (128–135)**Author Location** (B consensus)**Epitope** EIYKRWII**Epitope name** E18**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Donor MHC** A02, A03, B08, B62, Cw10, Cw7; A11, A29, B08, B44, Cw4, Cw7; A25, A32, B08, B14, Cw7, Cw8; A01, A03, B08, B14, Cw7, Cw8**Country** United States**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 4/9 individuals recognized this epitope, presented by HLA-B8.

**HXB2 Location** p24 (128–135)  
**Author Location** p24  
**Epitope** DIYKRWII  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Country** United Kingdom  
**Assay type** Tetramer binding, T-cell Elispot, Intracellular cytokine staining  
**Keywords** rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction  
**References** Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

**HXB2 Location** p24 (128–135)  
**Author Location** p24 (128–135)  
**Epitope** E1YKRWII  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Donor MHC** A1, A3, B35, B8  
**Country** United States  
**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, escape, variant cross-recognition or cross-neutralization  
**References** Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- DiYkrwii sequence was found in 12/17 clones after the initiation of therapy, while eYkrwii sequence was found in 5/17, and the peptide used to initially detect the response was not found, E1YKRWII. The less frequent clone was most often recognized. No dramatic shift towards escape was observed after the initiation of therapy.

**HXB2 Location** p24 (128–135)  
**Author Location** Gag  
**Epitope** E1YKRWII  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Country** Netherlands  
**Assay type** Tetramer binding, Flow cytometric T-cell cytokine assay  
**Keywords** binding affinity, rate of progression, escape, characterizing CD8+ T cells  
**References** Jansen *et al.* 2005

- Number and responsiveness of CD8 T-cells directed to different Gag peptides presented by HLA-A2, -B8 and B57 were compared. It was shown that T-cells specific for an HLA-B57 peptide responded to a higher extent and more readily to antigenic stimulation than those specific for HLA-A2 and -B8 peptides did. Moreover, it was shown that the higher functionality of B57-restricted T-cells was not correlated to higher

number of epitope escape mutations in A2- and B8-restricted T-cells.

- Tetramer decay experiments indicate that the HLA-B57 peptide has a higher half-life than the A2 and B8 peptides. The authors point out that CD8+ T cells with high binding affinity may require less help.
- In 1/2 B8+ individuals that were sequenced, 2 epitope variants were present: E1YKRWII and r1YKRWII, but the form E1YKRWII was found most often.

**HXB2 Location** p24 (128–135)  
**Author Location** Gag (260–267 B consensus)  
**Epitope** E1YKRWII

**Epitope name** E18

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A\*01, A\*11, B\*08, B\*15, Cw\*04, Cw\*07

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** escape, variant cross-recognition or cross-neutralization, optimal epitope

**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The E18 variant d1YKRWII was the only form of the epitope detected over a 5 year time period in this person. Elispot reactions were comparable between the autologous form and the B clade consensus form, E1YKRWII.

**HXB2 Location** p24 (128–135)  
**Author Location** p24

**Epitope** E1YKRWII

**Epitope name** B8-E18(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (128–135)

**Author Location**

**Epitope** EIYKRWII

**Immunogen**

**Species (MHC)** (B8)

**Keywords** review, immunodominance, escape, vaccine antigen design

**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection (recognized by >30% of subjects).

**HXB2 Location** p24 (128–135)

**Author Location**

**Epitope** EIYKRWII?

**Epitope name** EI8

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Country** United States, South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** memory cells

**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** p24 (128–135)

**Author Location**

**Epitope** EIYKRWII

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A1, A2; B38, B8

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.

- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.

- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** p24 (128–135)

**Author Location**

**Epitope** EIYKRWII

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, acute/early infection

**References** Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope EIYKRWII seen in 2 patients, underwent sequence changes.

**HXB2 Location** p24 (128–136)

**Author Location** Gag (260–268 SUMA)

**Epitope** EIYKRWIIL

**Epitope name** Gag EIL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.

- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** p24 (128–136)

**Author Location** Gag (260–268)

**Epitope** EIYKRWIIL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A2)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** p24 (128–136)

**Author Location** p24

**Epitope** EIYKRWIIL

**Subtype** B, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence in this person matched the known epitope.

**HXB2 Location** p24 (129–136)

**Author Location** p24 (263–270 SF2)

**Epitope** IYKRWIIL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**References** Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- IYKRWIIL bound to A\*2402 with medium strength, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

**HXB2 Location** p24 (129–138)

**Author Location** p24 (263–272 SF2)

**Epitope** IYKRWIILGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**References** Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- IYKRWIILGL bound to A\*2402 with medium strength, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

**HXB2 Location** p24 (129–138)

**Author Location** Gag (261–270)

**Epitope** IYKRWIILGL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A24)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** p24 (129–138)

**Author Location** p24

**Epitope** IYKRWIILGL

**Subtype** B, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

- Country** Democratic Republic of the Congo  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons  
**References** Geels *et al.* 2005
- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
  - This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence in this person matched the known epitope.
- HXB2 Location** p24 (129–138)  
**Author Location** p24 (263–272)  
**Epitope** IYKRWIILGL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Keywords** immunodominance  
**References** Betts *et al.* 2000
- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
  - 95 optimally-defined peptides from this database were used to screen for IFN $\gamma$  responses to other epitopes.
  - 1/11 of the A2+ individuals was B27 and responded to IYKRWIILGL.
- HXB2 Location** p24 (129–148)  
**Author Location** Gag (261–280)  
**Epitope** IYKLWIIILGLNKIVRMYSPT  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27, B62)  
**Donor MHC** A3, A31, B27, B38; A24, B27, B62  
**Assay type** Chromium-release assay  
**Keywords** genital and mucosal immunity  
**References** Musey *et al.* 2003
- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCR $\beta$  VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
  - CD8+ T cell clones directed at this epitope were derived from blood and rectum of one individual, and blood and semen of another. Both individuals are HLA-B27 positive, and within the peptide there is a B27 epitope that was recognized in the blood and rectum of the first patient, and in the blood of the second. A HLA-B62 epitope is also recognized in this peptide in the second individual, and the CD8+ T cells clones from both the blood and semen recognized this epitope.

- HXB2 Location** p24 (130–148)  
**Author Location** p24 (265–280 BRU)  
**Epitope** YKRWIILGLNKIVRMYSPT  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**References** Dadaglio *et al.* 1991
- Used as a positive control for HLA specificity.

- HXB2 Location** p24 (131–139)  
**Author Location** Gag (265–273)  
**Epitope** KRWIILGLN  
**Immunogen** HIV-1 infection  
**Species (MHC)** chimpanzee (Patr-B\*03)  
**References** Balla-Jhaghhoorsingh *et al.* 1999b
- Certain HLA-alleles have been associated with long-term survival – among them are HLA-B\*27 and HLA-B\*57.
  - Of more than 150 chimpanzees that have been reported to be infected with HIV-1, only one has developed AIDS.
  - CTL responses were studied in two HIV-1 infected chimpanzees that have strong CTL responses, and they were found to respond to highly conserved epitopes that are recognized in humans in the context of HLA-B\*27 and HLA-B\*57.
  - The human HLA protein which presents this Patr-B\*03 epitope is HLA B\*2705 but the amino acid sequences in the binding pockets of HLA-B\*2705 and Patr-B\*03 are distinctive.

- HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272)  
**Epitope** KRWIILGLNK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*27)  
**Keywords** HAART, ART  
**References** Huang *et al.* 2000
- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed.
  - Increases in gamma interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-gamma-production ELISPOT.
  - In 3/3 HLA A\*02, B\*27 individuals, the dominant response in gag measured by both gamma IFN production and T cell lysis was to the B27 epitope, KRWIILLGLNK, not the A2 SLYNTVATL epitope.

- HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272 SF2)  
**Epitope** KRWIILGLNK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*27)  
**References** McAdam *et al.* 1998
- Epitope invariant across clades A, B, C, and D.

- HXB2 Location** p24 (131–140)  
**Author Location** Gag  
**Epitope** KRWIILGLNK  
**Epitope name** KK10  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*27)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- Epitope KRWILGLNK is B\*27-, non-B\*57-restricted.
- An N271H variant, KRWILGLhK, was found in resting CD4+ T cells and could elicit immune responses.
- An L268M variant, KRWIImGLNK, found in plasma virus elicited at least as great immune response as wild type virus.

**HXB2 Location** p24 (131–140)**Author Location** p24 (131–140)**Epitope** KRWILGLNK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*27)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** binding affinity, subtype comparisons, acute/early infection**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, KRWILGLNK, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences.

**HXB2 Location** p24 (131–140)**Author Location** p24 (131–140)**Epitope** KRWILGLNK**Epitope name** KK10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*27)**Country** Switzerland**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** rate of progression, HLA associated polymorphism**References** Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than "other" HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by "other", non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also showed lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variants KkWIILGLNK and KRWIImGLNK/KRWIiGLNK at positions 2 and 6 were found. Phylogenetic analysis identified the leucine at position 6 to be under strong positive selective pressure.

**HXB2 Location** p24 (131–140)**Author Location****Epitope** KRWIILGLNK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*27)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** characterizing CD8+ T cells**References** Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.
- B\*27-restricted epitope KRWILGLNK does not correlate with any particular CTL maturation phenotype even though Controllers had similar viral loads.

**HXB2 Location** p24 (131–140)**Author Location** p24 (131–140)**Epitope** KRWIILGLNK**Epitope name** KK10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*02, B\*27)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other**Keywords** rate of progression, acute/early infection, memory cells**References** Sabbaj *et al.* 2007



- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope KK10, KRWIILGLNK, IFN-gamma was produced by CD127 lo cells in chronic patients without viremia. IL-2 and TNF-alpha were not secreted. In patients with early ART, IFN-gamma was secreted by both CD127 hi and lo cells before treatment but was maintained in CD127 hi cells after treatment. CD127 hi cells were responsible for producing IL-2 and TNF-alpha after ART.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (260–269 HIV-2)  
**Epitope** RRWIKLGLQK  
**Immunogen**  
**Species (MHC)** human (B\*2703)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*2703 epitope.

**HXB2 Location** p24 (131–140)  
**Author Location** p24  
**Epitope** KRWIILGGLNK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*2705)  
**Keywords** dynamics, acute/early infection  
**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- Tetramers with peptide variants KRWIILGGLNK and KRWIIMGLNK were used – CTL from most B27 donors recognize both variants, although one of the three subjects recognized only KRWIILGGLNK.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWIILGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272 LAI)  
**Epitope** KRWIILGGLNK

### Subtype B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*2705)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*2705 epitope.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272)  
**Epitope** KRWIILGLNK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*2705)  
**Keywords** escape  
**References** Kelleher *et al.* 2001b

- A mutation in 4/5 B\*2705 patients had substitution to lysine (K) at HIV-1 gag residue 264 (R264K), in three the change occurred late in infection – in one patient a substitution of glycine at HIV-1 gag residue 264 (R264G) was detected – these substitutions reduce binding to B27.
- The R264K mutations were associated with a L268M mutation that may be compensatory, and R264G occurred in conjunction with E260D.
- Positions 260, 264, and 268 all lie along one aspect of helix seven of the capsid protein, a region that is important for capsid self-association and assembly.
- R264G and R264K escape mutation outgrowth occurred in conjunction with high viral loads.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272)  
**Epitope** KRWIIMGLNK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*2705)  
**References** Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$

**HXB2 Location** p24 (131–140)  
**Author Location** p24  
**Epitope** KRWIILGLNK  
**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human (B\*2705)  
**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance  
**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** p24 (131–140)  
**Author Location** Gag (263–272)  
**Epitope** KRWIIILGLNK  
**Epitope name** KK10  
**Subtype** B  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease  
**Species (MHC)** human (B\*2705)  
**Donor MHC** A2, B27, B44, Cw2, Cw5  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay, Degranulation, CD107a and b cell surface mobilization  
**Keywords** vaccine-specific epitope characteristics, vaccine-induced epitopes, immunodominance, escape, TCR usage, characterizing CD8+ T cells  
**References** Betts *et al.* 2005

- A vaccinated HIV-negative individual exhibited features predicted to be necessary for vaccine-induced protection: killing ability, cytokine production, multifunctionality, proliferative capacity, polyclonality, memory phenotype, and a CD8 T-cell response directed against a highly immunodominant epitope correlated with long-term nonprogression. In spite of this, the subject became infected with HIV through homosexual contact. The subject progressed more rapidly than expected for an HLA-B27-positive individual.
- After infection, CD4+ and CD8+ T cells acquired functional characteristics typical of chronic HIV infection. The infecting virus escaped the vaccine-induced T-cell response with an R264G substitution, KgWIIILGLNK, which diminishes binding to B27, between the second and third year of infection.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (131–140)  
**Epitope** KRWIIILGLNK

**Epitope name** KRW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*2705)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells  
**References** Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B27-KRW is very strongly associated with delayed disease progression and its alanine-substituted variants are highly efficiently cross-recognized.

**HXB2 Location** p24 (131–140)  
**Author Location** Gag  
**Epitope** KRWIIILGLNK  
**Epitope name** KK10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*2705)  
**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** binding affinity, escape, dendritic cells, immune evasion  
**References** Lichterfeld *et al.* 2007a

- A variant of this epitope KK10, KRWIImGLNK (L6M), arises due to CTL escape and increases binding to Immunoglobulin-like transcript-4 (ILT4), leading to functional inhibition of DCs. Not only was KK10-L6M not recognized by CTLs but other variants like R2K and R2T were. During chronic infection, this variant recruited an alternative TCR $\alpha$  and  $\beta$ , being immunogenic enough to elicit a de novo CTL response. Finally, enhanced binding of this HLA-B\*2705-KK10-L6M complex to ILT4 occurred, resulting in an impairment of DC function as measured by the markers HLA-DR, CD83, CD40, CD180 and CD86.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272 LAI)  
**Epitope** KRWIIILGLNK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*2705, B27)  
**Keywords** review, rate of progression, immunodominance, escape  
**References** Goulder *et al.* 1997c; Goulder *et al.* 1997a  
 • HLA-B\*2705 is associated with slow HIV disease progression.  
 • 11/11 HLA-B\*2705 donors make a response to this epitope, usually an immunodominant response.

- This is a highly conserved epitope.
- The HLA-B\*2705 binding motif includes R at position 2, and L in the C-term position.
- Goulder *et al.* [1997a] is a review on CTL immune escape that discusses this epitope in the context of the difficulty in detection of immune escape – KRWIILGLNK and an R2K change, KKWIILGLNK, show little difference in titration curves, yet the K2 variants fail to bind to targets for more than 1 hour, while the R2 form can sensitize lysis by CTL for over 24 hours – minigene transfection experiments confirmed the importance of this for the CTL response.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (260–269 HIV-2)  
**Epitope** RRWILGLLQK

- Immunogen**  
**Species (MHC)** human (B27)  
**References** Brander & Walker 1996
- HIV-2, HLA-B\*2703, S. Rowland-Jones, pers. comm.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272 LAI)  
**Epitope** KRWIILGLNK  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Keywords** dendritic cells  
**References** Fan *et al.* 1997
- The capacity of dendritic cells to process and present antigen and stimulate anti-HIV-1 CTL memory responses was studied.

**HXB2 Location** p24 (131–140)  
**Author Location** Gag (263–272)  
**Epitope** KRWIILGLNK

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Keywords** epitope processing, dendritic cells  
**References** Zheng *et al.* 1999
- Protein delivery (gp160 LAV, p66 LAV, and p24 NY5) to human dendritic cells (DC) with liposomes provides enhanced memory CTL response relative to delivery of protein alone.
  - Chloroquine administration enhanced epitope presentation, and brefeldin A and peptide aldehyde inhibitors inhibited antigen presentation, suggesting epitopes were processed by classical proteasome pathway.
  - The CTL response to p24 was measured in individuals with a response to B27-KRWIILGLNK.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272 LAI)  
**Epitope** KRWIILGLNK  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Keywords** dynamics, TCR usage  
**References** Wilson *et al.* 1998a
- HIV+ individuals were followed longitudinally using MHC tetramers in combination with 14 anti-BV chain MAbs, and clonal expansion of HIV-specific T cells was followed *in vivo*.

- Seven HIV+ people were studied, and all showed expansions of particular TCR BV clones, often several, relative to uninfected controls.
- Three patients were followed in detail, TCR VB expansions persisted for 2 to 3 years, with occasional transient increases.

**HXB2 Location** p24 (131–140)  
**Author Location** p24  
**Epitope** KRWIILGLNK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Keywords** review  
**References** Rowland-Jones *et al.* 1997

- Described in this review as the first identified HIV CTL epitope.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272 LAI)  
**Epitope** KRWIILGLNK  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**References** Buseyne *et al.* 1993b

- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272 LAI)  
**Epitope** KRWIILGLNK  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Keywords** review  
**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272)  
**Epitope** KRWIIMGLNK

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**References** Klenerman *et al.* 1994

- Naturally occurring variant KRWIILGLNK may act as antagonist.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (263–272)  
**Epitope** KRWIIMGLNK

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**References** Klenerman *et al.* 1995

- Naturally occurring variant KRWIILGLNK may act as antagonist.

**HXB2 Location** p24 (131–140)  
**Author Location** p24 (265–274)  
**Epitope** KRWIILGLNK

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Keywords** dynamics, TCR usage  
**References** Moss *et al.* 1995

- In one individual, TCR usage changed over time indicating that new populations of CTL can be recruited.
- TCR usage showed a CTL clonal response to this epitope that persisted over 5 years.
- CTL clones specific for HIV epitopes may represent between 0.2 and 1% of the total CD8+ population of T cells.

**HXB2 Location** p24 (131–140)

**Author Location** p24 (265–276)

**Epitope** KRWIILGLNK

**Immunogen**

**Species (MHC)** human (B27)

**References** Carreno *et al.* 1992

- Included in HLA-B27 binding peptide competition study.

**HXB2 Location** p24 (131–140)

**Author Location** p24 (265–274 SF2)

**Epitope** KRWIILGLNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Keywords** dynamics, review, immunodominance, escape

**References** Goulder *et al.* 1997a; Phillips *et al.* 1991

- Longitudinal study of CTL escape mutants – little variation was observed in the immunodominant B27 epitope, relative to B8 epitope.
- Goulder *et al.* [1997a] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA B27 patients.

**HXB2 Location** p24 (131–140)

**Author Location** p24 (263–272)

**Epitope** KRWIILGLNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Keywords** review, escape

**References** Goulder *et al.* 1997a; Nietfeld *et al.* 1995

- Single point mutations were introduced and viral viability and CTL recognition tested – an Arg to Lys change at anchor position P2 abrogates binding to B27, but doesn't change viral viability *in vitro*.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

**HXB2 Location** p24 (131–140)

**Author Location** p24 (263–272)

**Epitope** KRWIIMGNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Keywords** escape

**References** Nowak *et al.* 1995

- Longitudinal study of CTL response and immune escape – the form KRWIILGNK was also found, and both forms stimulate CTL.

**HXB2 Location** p24 (131–140)

**Author Location** p24 (263–272)

**Epitope** KRWIILGNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Keywords** subtype comparisons

**References** Durali *et al.* 1998

- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia.
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested.
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag.
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef.
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env.
- One of the patients was shown to react to this epitope: KRWIILGNK.

**HXB2 Location** p24 (131–140)

**Author Location** p24 (263–272)

**Epitope** KRWIIMGLNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Keywords** review, immunodominance, escape

**References** Goulder *et al.* 1997f; Goulder *et al.* 1997a

- Six HLA-B27 donors studied make a strong response to this epitope.
- In 4/6 cases, this was the immunodominant or only CTL response.
- Two of the cases had an epitope switch to the form KKWIIMGLNK during a period of rapid decline to AIDS, following their asymptomatic period.
- The arginine to lysine switch is in an anchor residue, and results in immune escape due to severely diminished binding to the B27 molecule.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study in the context of CTL escape to fixation.

**HXB2 Location** p24 (131–140)

**Author Location** p24

**Epitope** KRWIILGLNK

**Immunogen**

**Species (MHC)** human (B27)

**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: RRWIQLGLQK – this epitope was not HIV-1 and HIV-2 cross-reactive.

**HXB2 Location** p24 (131–140)

**Author Location** Gag (263–)

**Epitope** KRWIILGLNK

**Immunogen** computer prediction

**Species (MHC)** (B27)

**Keywords** subtype comparisons

**References** Schafer *et al.* 1998

- This study uses EpiMatrix for T cell epitope prediction to identify possible HLA-B27 and A-2 CTL epitopes in HIV.
- Based on EpiMatrix predictions, 28 peptides were synthesized and tested using T2 binding assays for potential HLA A2 or B27 binding, and 12 of these were shown to bind to the predicted HLA molecule.
- Two of these 12 peptides had been previously identified as CTL epitopes: HLA-B27 KRWILGLNK and HLA-A2 ILKEPVHGV.
- This peptide sequence is not conserved between clades, but is found in most B clade isolates.

**HXB2 Location** p24 (131–140)**Author Location** p24 (263–282)**Epitope** KRWILGLNK**Immunogen** HIV-1 infection**Species (MHC)** human (B27)**References** Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population.
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs.
- Epitope sequences were deduced from larger reactive peptides based on HLA binding motifs – XRXXXXXXXXK is a B\*2705 binding motif.

**HXB2 Location** p24 (131–140)**Author Location** p24 (265–274 SF2)**Epitope** KRWILGLNK**Immunogen** HIV-1 infection**Species (MHC)** human (B27)**Keywords** HAART, ART, acute/early infection**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B27+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/1 group 3.

**HXB2 Location** p24 (131–140)**Author Location** p24 (263–272)**Epitope** KRWILGLNK**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human (B27)**Keywords** HIV exposed persistently seronegative (HEPS)**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Subject ML 1760 had an A2 response to ILK(D/E)PVHGV prior to seroconversion, and gained responses to epitopes A2 SL(F/Y)NTVATL and B27 KRWII(L/M)GLNK post-seroconversion.

**HXB2 Location** p24 (131–140)**Author Location** p24 (131–140)**Epitope** KRWILGLNK**Immunogen** HIV-1 infection**Species (MHC)** human (B27)**References** Day *et al.* 2001**HXB2 Location** p24 (131–140)**Author Location** p24 (260–299)**Epitope** RRWQLGLQK**Immunogen** HIV-1 infection**Species (MHC)** human (B27)**References** Day *et al.* 2001**HXB2 Location** p24 (131–140)**Author Location** p24 (131–140)**Epitope** KRWILGLNK**Epitope name** KK10**Immunogen** HIV-1 infection**Species (MHC)** human (B27)**Keywords** responses in children, mother-to-infant transmission, immunodominance, escape, acute/early infection**References** Goulder *et al.* 2001b

- 85% of B27+ adults have CTL that recognize this epitope, but only 2/6 children did.
- Responses to this dominant B27-restricted Gag epitope are present during the time of decreasing viral load in acute infection.
- Three children who shared B27 with their mothers did not respond to this epitope and inherited escape mutations from their mothers.
- A transmitted R132T anchor residue mutation abrogated binding to B27.
- In the three children infected with the non-binding KK10 variants, the dominant CTL specificity was still HLA-B27-restricted, but it was directed against an epitope in p17, IRL-RPGGKK, only rarely recognized in adults when KRWIIILGLNK is the dominant response.

- Mutations in this epitope were observed in autologous clones of subjects who were B27-positive with a higher frequency than those who were B27-negative ( $P = 0.0005$ )
- These mutations are being sexually transmitted in adult infections.

**HXB2 Location** p24 (131–140)

**Author Location**

**Epitope** KRWIILGLNK

**Epitope name** Gag-KK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B27, 2/3 (66%) recognized this epitope.

**HXB2 Location** p24 (131–140)

**Author Location** p24 (263–272 LAI)

**Epitope** KRWIIMGLNK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Keywords** HAART, ART, epitope processing, immunodominance

**References** Kelleher *et al.* 2001a

- Ritonavir (RTV) inhibits chymotryptic activity in the 20S proteasome *in vitro*, as does Saquinavir (SQV) to a lesser extent; Indinavir (IDV) does not. Thus there is concern protease inhibitors may adversely affect CTL epitope processing, but this paper indicates that processing is not inhibited at therapeutically relevant concentrations of RTV when the proteasome is functioning in an intracellular context.
- RTV did not reduce antigen presentation and concentration of the two immunodominant Gag CTL epitopes (KRWIIMGLNK (B27) and SLYNTVATL (A2)).
- RTV did not inhibit the processing and assembly of HLA-B35 or -A2, which are assembled with a rapid and moderate time course, respectively, or of HLA-A3, -B27 and -B39.

**HXB2 Location** p24 (131–140)

**Author Location** p24

**Epitope** KRWIILGLNK

**Epitope name** B27-KK10(p24)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Donor MHC** A24, B27, B7; A30, A32, B18, B27

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.

- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.

- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.

- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.

- Breakdowns of epitope responses were shown for 4 individuals. Patient C displayed the greatest response to B27-KK10(p24), and in decreasing order also responded to A24-RW8(Nef), B7-IL9(gp41), A24-RL9(gp41), A24-YL8(gp41), and B7-TM9(Nef). Patient D also displayed the greatest response to B27-KK10(p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

**HXB2 Location** p24 (131–140)

**Author Location** Gag (263–272)

**Epitope** KRWIILGLNK

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Donor MHC** B27

**Keywords** subtype comparisons

**References** Currier *et al.* 2002a

- Cross-reactive responses were found in PBMC isolated from individuals infected with either B or CRF01\_AE clade viruses, as determined by Elispot assays of target cells expressing recombinant vaccinia viruses expressing HIV-1 gag, env, nef and pol from many clades.
- Subject AIHP-6 (Thai, CDF01-AE infected) recognized this epitope. This subject showed cross-subtype CTL responses to gag constructs derived from subtypes A, B, C, D, F, G, and H, and this epitope was perfectly preserved in all of these but subtype A which had the sequence KRWMILGLNK.
- This subject didn't respond to a Gag CRF01 sequence which had a R->K mutation in position 2.

**HXB2 Location** p24 (131–140)

**Author Location** Gag

**Epitope** KRWIILGLNK

**Epitope name** KK10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Donor MHC** A26, B27

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, rate of progression, immunodominance, escape

**References** Feeney *et al.* 2004

- Viral load in a perinatally infected child remained low until emergence of an escape variant (kTwiiIgLnk) in the immunodominant CTL epitope KRWIIILGLNK when the child was 7.4 years old. The emergence of this escape mutation was followed by an increase in viremia and an increase in the number of targeted CTL epitopes, measured again when the child was 9.2 years old. The timing suggests that the loss of recognition of this epitope may have resulted in the subsequent loss of immune control.
- The mutation krwiiMglnk has been suggested to be compensatory and required for the emergence of the previously described escape mutation kKwiiMglnk (Kelleher 2001). The L136M mutation does appear in this child, but not in conjunction with the R132T escape mutation.

**HXB2 Location** p24 (131–140)

**Author Location**

**Epitope** KRWIIMGLNK

**Epitope name** KK10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Keywords** review, responses in children, vaccine-specific epitope characteristics, rate of progression, escape

**References** Goulder & Watkins 2004

- This paper is a review of the role of CTL in HIV infection, and it uses KK10 as an example of an epitope that has late escape mutations associated with loss of immune control of the virus and decline to AIDS.
- A study where a vaccine response to KK10 was stimulated in a individual who subsequently got infected and had rapid escape from the KK10 response and an unexpectedly high steady state viral load for a B27+ person is recounted as a cautionary note regarding the delicate balance of effects that might contribute to CTL mediated immune control.

**HXB2 Location** p24 (131–140)

**Author Location** Gag

**Epitope** KRWIIILGLNK

**Epitope name** KK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 6, krwiiMglnk, was found in the most polymorphic residue in the epitope. This was shared between clades B and C. One escape mutation, at position 2, kTwiiIgLnk, was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** p24 (131–140)

**Author Location** Gag (263–272 BRU)

**Epitope** KRWIIILGLNK

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02\_AG-infected Ivorians, and 3/9 B-infected French subjects.

**HXB2 Location** p24 (131–140)

**Author Location** p24

**Epitope** KRWIIILGLNK

**Epitope name** KK10

**Immunogen**

**Species (MHC)** (B27)

**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion

**References** Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** p24 (131–140)

**Author Location** Gag (263–272)

**Epitope** KRWIIILGLNK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Country** Barbados

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection

**References** Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- A B27 escape footprint was passed from a B27+ father to his partner, who then passed the variant to their child. KRWIIILGLNK is the B consensus form of this epitope, the paternal form was KqWIIiGLNK, the maternal form, KqWvImGLNK, and this was the form passed on to the child.

**HXB2 Location** p24 (131–140)

**Author Location** Gag (263–272)

**Epitope** KRWIIILGLNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Country** Australia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, rate of progression, immunodominance, escape

**References** Ammaranond *et al.* 2005

- B27-positive subjects have an immunodominant response to Gag epitope KRWILGLNK, with R264 KrWILGLNK being a crucial anchor residue. Among a group of 20 long-term non-progressive B27-positive subjects, 14 carried wild-type sequence, 5 carried known escape mutants (K264 or G264), and 1 carried a novel Q264 mutant. This mutant was also shown to be a likely escape mutation. These escape mutations all lower the affinity for B27 binding; the Q264 variant has 30-fold lower binding affinity.

**HXB2 Location** p24 (131–140)

**Author Location** p24

**Epitope** KRWILGLNK

**Epitope name** B27-KK10(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.
- This epitope, KRWILGLNK (KK10), elicits the HLA-B27 restricted response that is most dominant of the immune responses generated.

**HXB2 Location** p24 (131–140)

**Author Location** p24 (131–140)

**Epitope** KRWIIMGLNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Donor MHC** A1, A3, B\*2705, B35; A2, A22, B\*2705, B35

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rates for this epitope, KRWIIMGLNK, were found in 3 subjects to be 0.002, 0.001 and 0.010/day, with SEs of 0.003, 0.003 and 0.011 respectively.
- The escape mutation was R132K in all cases.

**HXB2 Location** p24 (131–140)

**Author Location** p24

**Epitope** KRWIIMGLHK

**Epitope name** KK10 (263-272)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Donor MHC** A2, A68, B27, B35

**Country** France

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, immunodominance, characterizing CD8+ T cells

**References** Almeida *et al.* 2007

- Since it is suggested that a single response to B27-KK10 epitope may be responsible for the association of HLA-B\*2705 patients with AIDS-free survival, B27-KK10-specific CTLs were compared to other HLA-specific CTLs in phenotype, function, clonal diversity, and antigen sensitivity in 47 treatment-naive infected slow or nonprogressing patients.
- cVL, the cell-associated viral load (number of infected cells harboring HIV DNA) correlated inversely with Gag-specific CTLs. This was most significant in HLA-B27 donors, and KK10 was identified as the peptide generating strongest CTL responses.
- B27-KK10-specific CTLs had no significant phenotypic differences from other epitope-specific CTLs upon testing a large panel of markers; however, they released higher proportions of IFN-gamma, TNF-alpha, MIP-1beta and CD107a upon antigenic stimulation.
- Both B27-KK10-specific and other HLA-specific CTLs had strikingly consistent domination of single clonotypes, as shown by analyses of TCRB gene expression. B27-KK10-specific CTLs showed no preferential usage of CDR3 motifs, indicating that they could be recognized by diverse clonotypes with differing binding properties. Over several years, B27-KK10-specific CTLs changed their dominant clonotype as compared to other CTLs. This temporal dominant clonal turnover was attributed to a decline in replicative capacity of



the dominant clonotype as seen by increases in CD57 expression, which is linked to replicative senescence.

- Studies involving functional avidity and different HLA-restricted responses proved that B27-KK10 responses had highest avidity. An inverse correlation between patient cVL and functional avidity of both dominant and highest subdominant responses suggested that functional avidity correlates with capacity to control HIV replication via infected cell elimination.
- Using the example seen in one patient, the authors stress the importance of maintaining protective stimulating activity of CTLs. When control by dominant clonotypes is lost, as in viral escape, ensuing viral replication is rapid.
- In one B27-positive patient studied, the dominantly-targeted epitope sequence changed over time from KRWIIMGLHK to KRWIILGLNK.

**HXB2 Location** p24 (131–140)

**Author Location**

**Epitope** KRWIILGLNK

**Epitope name** KK10

**Immunogen** HIV-1 infection, peptide-HLA interaction

**Species (MHC)** human, mouse (B27)

**Assay type** Tetramer binding, Chromium-release assay, HLA binding

**Keywords** assay standardization/improvement, review, epitope processing, escape, structure, optimal epitope

**References** McMichael 2007a

- This historical essay recounts the discovery of antigenic peptide processing by MHC-I. New techniques, the first epitope in HIV (KK10), epitope identification, escape mutations and HLA type are discussed with respect to CTLs in HIV infection control.

**HXB2 Location** p24 (131–140)

**Author Location**

**Epitope** KRWIILGLNK

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B27)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p24 (131–140)

**Author Location** p24

**Epitope** KRWIIMGLNK

**Epitope name** KK10 (263-272)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Donor MHC** A2, A32, B27, B39; A24, A3, B27, B7; A3, A32, B27, B35

**Country** France

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, immunodominance, characterizing CD8+ T cells

**References** Almeida *et al.* 2007

- Since it is suggested that a single response to B27-KK10 epitope may be responsible for the association of HLA-B\*2705 patients with AIDS-free survival, B27-KK10-specific CTLs were compared to other HLA-specific CTLs in phenotype, function, clonal diversity, and antigen sensitivity in 47 treatment-naive infected slow or nonprogressing patients.
- cVL, the cell-associated viral load (number of infected cells harboring HIV DNA) correlated inversely with Gag-specific CTLs. This was most significant in HLA-B27 donors, and KK10 was identified as the peptide generating strongest CTL responses.
- B27-KK10-specific CTLs had no significant phenotypic differences from other epitope-specific CTLs upon testing a large panel of markers; however, they released higher proportions of IFN-gamma, TNF-alpha, MIP-1beta and CD107a upon antigenic stimulation.
- Both B27-KK10-specific and other HLA-specific CTLs had strikingly consistent domination of single clonotypes, as shown by analyses of TCRB gene expression. B27-KK10-specific CTLs showed no preferential usage of CDR3 motifs, indicating that they could be recognized by diverse clonotypes with differing binding properties. Over several years, B27-KK10-specific CTLs changed their dominant clonotype as compared to other CTLs. This temporal dominant clonal turnover was attributed to a decline in replicative capacity of the dominant clonotype as seen by increases in CD57 expression, which is linked to replicative senescence.
- Studies involving functional avidity and different HLA-restricted responses proved that B27-KK10 responses had highest avidity. An inverse correlation between patient cVL and functional avidity of both dominant and highest subdominant responses suggested that functional avidity correlates with capacity to control HIV replication via infected cell elimination.
- Using the example seen in one patient, the authors stress the importance of maintaining protective stimulating activity of CTLs. When control by dominant clonotypes is lost, as in viral escape, ensuing viral replication is rapid.
- In one B27-positive patient studied, the dominantly-targeted epitope sequence changed over time from KRWIIMGLNK to KRWIILGLNK.

**HXB2 Location** p24 (131–140)

**Author Location** Gag

**Epitope** KRWIILGLNK

**Epitope name** KK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27, B35, B57)

**Country** Australia, Canada, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** rate of progression, immunodominance, optimal epitope

**References** Streeck *et al.* 2007a

- To characterize HIV-1 proteome areas that are targeted in early, effective CTL responses, two cohorts were studied. Responses in early infection were against fewer epitopes and of lower magnitude than during chronic infection. While no region of the proteome was favored, Nef was the predominant target based on length of proteins. When based on the expression of protective versus nonprotective HLA I alleles, it was found that HLA-B27 and -57 possessing slow progressors to disease directed the majority of their responses to Gag in early infection, as opposed to those with HLA-B\*3501 or B\*3502, i.e. rapid progressors to AIDS, who had negligible responses to Gag. As compared with HLA-B57-/B27-subjects and HLA-B35 subjects, HLA-B57+/27+ subjects responded most to the p24 component of Gag. By using overlapping peptides within Gag p24, two were picked as being consistently targeted, and both contained previously described epitopes TW10 and KK10.
- KRWIILGLNK, epitope KK10, is one of two immunodominant epitopes targeted during early infection in long term non-progressors to AIDS. Only in later phases of infection, after accumulation of compensatory mutations do most subjects develop variants.

**HXB2 Location** p24 (131–140)

**Author Location**

**Epitope** KRWIILGLNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B2705)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KRWIILGLNK elicited a magnitude of response of 1510 SFC with a functional avidity of 0.001nM.

**HXB2 Location** p24 (131–140)

**Author Location** Gag (263–272 LAI)

**Epitope** KRWIILGLNK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.

- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag.

**HXB2 Location** p24 (131–140)

**Author Location** Gag (263–272 B27)

**Epitope** KRWIILGLNK

**Epitope name** KK10 (263-272)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** review, immunodominance, escape, dendritic cells, immune evasion, viral fitness and reversion, compensatory mutation

**References** McMichael 2007b

- This commentary summarizes work by Lichtenfeld *et al.* [JEM Vol. 204: 2785-7 (2007)]. HLA-B27 restricted CTLs presented with epitope KK10 (KRWIILGLNK) are known to keep infection at bay in LTPs. However, a triple mutation resulting in viral escape can occur after several years. The mutations are L268M, R264K(T/G) and S173A. L268M occurs early in infection and becomes fixed when bound to HLA-B27, conferring unknown viral advantage that is suggested to be due to its 3-fold higher affinity for ILT4. This may result in impaired DC and monocyte function. It is thought that the triple mutations compensate for each other, stabilizing them.

**HXB2 Location** p24 (131–140)

**Author Location**

**Epitope** KRWIILGLNK

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120

*boost Strain:* Other *HIV component:* gp160

**Species (MHC)** human

**Donor MHC** A3, A33; B15 (63), B27

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** p24 (131–140)

**Author Location**

**Epitope** KRWIILGLNK

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, acute/early infection  
**References** Lichterfeld *et al.* 2007b
- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
  - None of the target epitopes, including this epitope KRWIILGLNK seen in 1 patient, underwent sequence changes.
- HXB2 Location** p24 (131–140)  
**Author Location** Gag (263–272)  
**Epitope** KRWIILGLNK  
**Epitope name** KK10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** Other  
**Keywords** escape, acute/early infection, immune evasion, viral fitness and reversion, optimal epitope, compensatory mutation  
**References** Schneidewind *et al.* 2007
- Epitope KK10 in HLA-B27 slow progressors to disease varies late in infection, leading to AIDS. The predominant escape mutation for this epitope is R264K, and it severely compromises virus replication, late in reverse transcription but unrelated to capsid stability. This can be restored by an in vivo upstream compensatory mutation, S173A and modulation of CypA binding in the presence of cyclosporine A. However, the first mutation to arise is the L268M, a prerequisite compensatory mutation to R264K.
  - Four HLA-B27 subjects' virus were sequenced longitudinally to find that the KK10 epitope mutates from KRWIILGLNK (WT) to KkWIILGLNK (R264K), KRWIILGmNK (L268M), KkWIImGLNK (R264K/L268M), KRWIILGLNK (S173A), KkWIILGLNK (S173A/R264K), KkWIImGLNK (S173A/R264K/L268M) and KkWIImGLNK (A237T on R264K/L268M).
- HXB2 Location** p24 (131–142)  
**Author Location** p24 (265–276)  
**Epitope** KRWIILGLNKIV  
**Immunogen** peptide-HLA interaction  
**Species (MHC)** human (B27)  
**References** Jardetzky *et al.* 1991
- Epitope examined in the context of peptide binding to HLA-B27.
- HXB2 Location** p24 (131–142)

- Author Location** p24 (263–274 LAI)  
**Epitope** KRWIILGLNKIV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Keywords** dendritic cells  
**References** Fan *et al.* 1997
- The capacity of dendritic cells to process and present antigen and stimulate anti-HIV-1 CTL memory responses was studied.
- HXB2 Location** p24 (131–142)  
**Author Location** p24 (131–142)  
**Epitope** KRWIILGLNKIV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**References** Ferrari *et al.* 2000
- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.
- HXB2 Location** p24 (131–142)  
**Author Location** p24 (265–275)  
**Epitope** KRWIILGLNKIV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B27)  
**Donor MHC** A2, A24, B27, B62  
**Country** United Kingdom  
**Assay type** Flow cytometric T-cell cytokine assay, Other  
**Keywords** HAART, ART, immunodominance, TCR usage, memory cells  
**References** Weekes *et al.* 2006
- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintenance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.
- HXB2 Location** p24 (131–145)  
**Author Location** p24 (263–277 LAI)  
**Epitope** KRWIILGLNKIVMRY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A33)  
**References** Buseyne *et al.* 1993b
- Clustering of Gag p24 CTL epitopes recognized in 29 HIV-infected people.
- HXB2 Location** p24 (131–145)  
**Author Location** p24 (266–277)  
**Epitope** KRWIILGLNKIVRMV  
**Immunogen** vaccine  
**Vector/Type:** vaccinia *HIV component:* Gag

**Species (MHC)** human (B27)

**References** Nixon *et al.* 1988

- Gag CTL epitope mapped with rec gag-vaccinia and synthetic peptides.
- This was the first HIV-1 epitope to be mapped.

**HXB2 Location** p24 (131–145)

**Author Location** p24 (266–277 LAI)

**Epitope** KRWIILGLNKIVRMRY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Meyerhans *et al.* 1991

- Longitudinal study showing persistence of epitope despite CTL activity.

**HXB2 Location** p24 (131–145)

**Author Location** p24 (265–279)

**Epitope** KRWIILGLNKIVRMRY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Nixon *et al.* 1990; Rowland-Jones *et al.* 1999

- HIV-1 and HIV-2 cross-reactive CTL clone, highly conserved epitope.
- Reviewed in Rowland-Jones99, notes that it did not appear cross-reactive with HIV-2 in Rowland-Jones98, HIV-2 form: RRWQLGLQK.

**HXB2 Location** p24 (131–145)

**Author Location** p24 (SF2)

**Epitope** KRWILGLNKIVRMRY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ African American living in Boston with unknown HLA – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRL-RPGGKKKYKLGK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDL-NTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (131–145)

**Author Location** p24 (131–145 HXB2)

**Epitope** KRWIILGLNKIVRMRY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p24 (131–146)

**Author Location** p24 (265–279)

**Epitope** KRWIILGLNKIVRMRYC

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Bouillot *et al.* 1989

- HLA-B27 restricted epitope also binds to HLA-A2 and HLA-B37 in solid phase assay.

**HXB2 Location** p24 (131–150)

**Author Location** p24 (265–284 SF2)

**Epitope** KRWIILGLNKIVRMYSPTSIS

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62?)

**References** van Baalen *et al.* 1993

- Gag CTL epitope precursor frequencies estimated.

**HXB2 Location** p24 (131–150)

**Author Location** p24 (263–282 SF2)

**Epitope** KRWIILGLNKIVRMYSPTSIS

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 A-2 had CTL response to this peptide.
- The responding subject was HLA-A3, A32, B51, B62.

**HXB2 Location** p24 (131–152)

**Author Location** p24 (263–284 BH10)

**Epitope** KRWIILGLNKIVRMYSPTSISLD

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**References** Johnson *et al.* 1991

- Gag CTL response studied in three individuals.

**HXB2 Location** p24 (132–140)**Author Location** Gag (261–280)**Epitope** RWIILGLNK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B27)**Donor MHC** A24, A33, B14, B27; A2, A32, B27, B62**Assay type** Chromium-release assay**Keywords** genital and mucosal immunity**References** Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCR $\beta$  VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones that recognize this epitope were derived from both blood and cervix from a woman, and the blood and semen from a man.

**HXB2 Location** p24 (132–145)**Author Location** Gag**Epitope** KWILGLNKIVRMY**Immunogen** HIV-1 infection**Species (MHC)** human (B27)**Keywords** TCR usage**References** Weekes *et al.* 1999b

- Peptide 728: Almost all CD8+ T cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed the CD28 depleted cell population.
- HIV CTL responses to 3 Env and 2 Gag peptides were studied.
- The clonal composition of the TCR V $\beta$  responses were studied and was found to be highly focused, with one TCR beta-chain sequence tending to dominate the peptide-specific response – clones to this epitope were V $\beta$ 22.1.

**HXB2 Location** p24 (132–145)**Author Location** Gag**Epitope** KWILGLNKIVRMY**Immunogen** HIV-1 infection**Species (MHC)** human**References** Weekes *et al.* 1999a

- Peptide 728: Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28- CD8+ CTLp populations.

**HXB2 Location** p24 (134–142)**Author Location** Gag (Henan isolate)**Epitope** IILGLNKIV**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** China**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p24 (134–143)**Author Location** Gag (266–275)**Epitope** IILGLNKIVR**Subtype** B**Immunogen** vaccine*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21**Species (MHC)** human (A11, A3)**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** p24 (134–143)**Author Location** p24 (subtype B)**Epitope** IILGLNKIVR**Subtype** B**Immunogen** HIV-1 exposed seronegative**Species (MHC)** human (A33)**Keywords** subtype comparisons**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B and D clade viruses.

**HXB2 Location** p24 (135–142)**Author Location** p24 (135–142)**Epitope** ILGLNKIV**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201)**Country** India**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope ILGLNKIV is highly conserved across clades (100% to subtype A, >60% to subtype D).

**HXB2 Location** p24 (135–142)

**Author Location** Gag (267–274)

**Epitope** ILGLNKIV

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A2)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** p24 (135–142)

**Author Location** Gag (267–274 HXB2)

**Epitope** ILGLNKIV

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2, A3)

**Country** Viet Nam

**Assay type** HLA binding

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.

- ILGLNKIV is the epitope in the HXB2 reference strain sequence, and is also the most common form in CRF01.

**HXB2 Location** p24 (135–142)

**Author Location** p24 (135–142)

**Epitope** ILGLNKIV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*27)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, ILGLNKIV, was detected within overlapping peptide PVGEIYKRWIIILGLNKIV.

**HXB2 Location** p24 (135–143)

**Author Location** Gag (267–275)

**Epitope** ILGLNKIVR

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A11, A3)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** p24 (135–145)

**Author Location** Gag (267–277)

**Epitope** ILGLNKIVRMY

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (B7 supertype)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.
- A response to this peptide was induced in three patients after immunization with lipopeptides alone (no adjuvant) after the third and the fourth boost, and induced in two patients after immunization with lipopeptides and QS21 adjuvant after the third boost. Variant IyGLNKIVRMY was also recognized in two patients.

**HXB2 Location** p24 (136–145)

**Author Location** p24 (268–277 LAI)

**Epitope** LGLNKIVRMY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** review

**References** McMichael & Walker 1994

- Predicted from larger peptide.
- Review of HIV CTL epitopes.
- Also P. Johnson, pers. comm.

**HXB2 Location** p24 (136–146)

**Author Location** p24 (271–281)

**Epitope** LGLNKIVRMYS

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** TCR usage

**References** Lubaki *et al.* 1997

- Eighty two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response.
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA molecules, indicating a polyclonal response.
- A subject who was B62+ had CTL that recognized this peptide, p17 KIRLRPGGKKKYKL, and one additional unknown epitope.
- The two clones that recognized this epitope used two different V $\beta$  genes, further demonstrating a polyclonal response.

**HXB2 Location** p24 (136–146)

**Author Location** p24 (136–146)

**Epitope** LGLNKIVRMY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (136–146)

**Author Location** Gag (275–285)

**Epitope** LGLNKIVRMY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p24 (136–150)

**Author Location** p24 (136–150 HXB2)

**Epitope** LGLNKIVRMYSPSTSI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized—the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized. A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p24 (137–145)

**Author Location** p24 (137–145)

**Epitope** GLNKIVRMY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*15, B\*62)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, subtype comparisons, acute/early infection

**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, GLNKIVRMY, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences.

**HXB2 Location** p24 (137–145)

**Author Location** p24 (272–280 LAI)

**Epitope** GLNKIVRMY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1501 epitope.

**HXB2 Location** p24 (137–145)

**Author Location** Gag (269–277 SUMA)

**Epitope** GLNKIVRMY

**Epitope name** Gag GY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1501)

**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.

- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.

- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** p24 (137–145)

**Author Location** p24 (137–145)

**Epitope** GLNKIVRMY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1501)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, GLNKIVRMY, was predicted to be restricted by HLA A\*0203, A1, B\*1501.

**HXB2 Location** p24 (137–145)

**Author Location** Gag (B con)

**Epitope** GLNKIVRMY

**Epitope name** GY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** variant cross-recognition or cross-neutralization

**References** Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN ELISPOT responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that



persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.

- 1 subject recognized this epitope with intermediate functional avidity. The autologous sequence matched the B consensus.

**HXB2 Location** p24 (137–145)

**Author Location** p24

**Epitope** GLNKIVRMY

**Epitope name** B15-GY9(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (137–145)

**Author Location**

**Epitope** GLNKIVRMY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B1501)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope GLNKIVRMY elicited a magnitude of response of 510 SFC with a functional avidity of 0.25nM.

**HXB2 Location** p24 (137–145)

**Author Location**

**Epitope** GLNKIVRMY

**Immunogen** HIV-1 infection, vaccine

**Vector/Type:** canarypox, canarypox prime with recombinant protein boost **Strain:** B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen **HIV component:** Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B27)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p24 (137–145)

**Author Location** p24 (272–280 LAI)

**Epitope** GLNKIVRMY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** review, escape

**References** Goulder *et al.* 1997a

- This paper is a review of CTL and immune evasion, but it presents a study of a shift from an HLA-A\*0201 response to SLYNTVATL, to a B62 response to GLNKIVRMY.
- As long as a strong CTL response to SLYNTVATL was evident, the epitope variants SLFNTVATL or SLYNTIATL dominated the viral population – eventually the CTL response to the index peptide became undetectable, the CTL response shifted to a focus on GLNKIVRMY, and the index peptide SLYNTVATL once again established itself as the dominant form.

**HXB2 Location** p24 (137–145)

**Author Location** p24 (SF2)

**Epitope** GLNKIVRMY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ African American living in Boston – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (137–145)  
**Author Location** p24 (267–277 SF2)  
**Epitope** GLNKIVRMY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B62+ individuals that had a CTL response to this epitope broken down by group: 0/1 group 1, 0/1 group 2, and 1/1 group 3.

**HXB2 Location** p24 (137–145)  
**Author Location** p24 (137–145)

**Epitope** GLNKIVRMY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** immunodominance

**References** Day *et al.* 2001

- No immunodominant responses were detected to four B62-restricted epitopes tested.

**HXB2 Location** p24 (137–145)  
**Author Location** p24 (137–145)

**Epitope** GLNKIVRMY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Donor MHC** A1, A3, B62, B8, Cw3, Cw7

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15–92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN- $\gamma$  secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.

- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** p24 (137–145)  
**Author Location** Gag (269–277)

**Epitope** GLNKIVRMY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Donor MHC** A2, A24, B27, B62

**Assay type** Chromium-release assay

**Keywords** TCR usage, genital and mucosal immunity

**References** Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCR $\beta$  VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood, rectum and semen.
- The TCR $\beta$  VDJ rearrangement of the CTL clones was V $\beta$ 22S1DJ1.2, demonstrating expansion of CTL clones in all three compartments from the same progenitor cell.

**HXB2 Location** p24 (137–145)  
**Author Location** Gag (269–277)

**Epitope** GLNKIVRMY

**Epitope name** GY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Donor MHC** A\*01, A\*11, B\*08, B\*15, Cw\*04, Cw\*07

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** escape, optimal epitope

**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.

- The autologous form of the GY9 matched the B clade consensus form of the epitope, GLNKIVRMY, throughout the 5 years of study.

**HXB2 Location** p24 (137–145)  
**Author Location** Gag (269–277 HXB2)  
**Epitope** GLNKIVRMY  
**Subtype** B, CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B62)  
**Country** Viet Nam  
**Assay type** HLA binding  
**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design  
**References** Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- GLNKIVRMY is the epitope in the HXB2 reference strain sequence, and is also the most common form in CRF01.

**HXB2 Location** p24 (137–145)  
**Author Location** p24 (C consensus)  
**Epitope** GLNKIVRMY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A2, B\*5802, B62, Cw4, Cw6  
**Keywords** subtype comparisons, immunodominance  
**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ South African living in Durban, HLA A2/- B5802/62 Cw4/6 – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71–85), SALSEGATPQDLNLTMLNTVG (p24 41–60), and WEKIRL-RPGGKKKYKLG (p17 16–30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20–36), ELRSLYNTVATLYCV (p17Gag 74–88), SALSEGATPQDLNLTMLNTVG (p24 41–60), FRDYVDRFFKTLRAEQA (p24 161–177), and SILDIKQGKPEFRDY (p24 149–164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (142–150)  
**Author Location**  
**Epitope** VRMYSPVSI  
**Epitope name** VI9  
**Immunogen**  
**Species (MHC)** human (Cw\*18)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a Cw18 epitope.

**HXB2 Location** p24 (142–150)  
**Author Location** (C consensus)  
**Epitope** VRMYSPVSI  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*1801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- VRMYSPVSI is an optimal epitope.

**HXB2 Location** p24 (142–150)  
**Author Location** p24 (142–150)  
**Epitope** VRMYSPVSI  
**Immunogen** peptide-HLA interaction  
**Species (MHC)** human (Cw\*1801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** optimal epitope  
**References** Honeyborne *et al.* 2006

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B\*3910, B\*4201, B\*8101 and Cw\*1801, by motif inference. HLA-A\*2902 was found to overlap those of A1 and A24 supertypes.
- VRMYSPVSI was the optimal epitope for HLA-Cw\*1801 with variants VRMYSPVS, RMYSPVSI, VRMYSPVSI, iVRMYSPVSI having been tested.

**HXB2 Location** p24 (143–150)  
**Author Location** p24 (273–283 IIIB)  
**Epitope** RMYSPVSI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5201)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5201 epitope.

**HXB2 Location** p24 (143–150)  
**Author Location** p24 (273–283 IIIB)  
**Epitope** RMYSPVSI  
**Epitope name** SL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B52)  
**Keywords** epitope processing, immunodominance, escape  
**References** Brander *et al.* 1999

- Multiple natural variations in the SL9 flanking regions of the immunodominant epitope SLYNTVATL were tested and found not to adversely affect CTL recognition or prevent epitope processing, suggesting that viral escape from the HLA-A\*0201-restricted CTL response against SLYNTVATL is probably not linked to variations in the flanking regions of this epitope.

- The CTL response to RMYSPSTSI was used as a control.

**HXB2 Location** p24 (143–150)  
**Author Location** p24 (273–283 IIIB)  
**Epitope** RMYSPSTSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B52)

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- No variants of this epitope were found in a non-transmitting mother that had a CTL response to this epitope.

**HXB2 Location** p24 (143–150)  
**Author Location** p24 (143–150)  
**Epitope** RMYSPSTSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B52)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (143–150)  
**Author Location** Gag (275–282)  
**Epitope** RMYSPSTSI

**Epitope name** RI8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B52)

**Donor MHC** A\*02, A\*68, B\*14, B\*52, Cw\*08, Cw\*12

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** escape, optimal epitope

**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- A form of this epitope that elicited a diminished Elispot response, RMYSPvSI, dominated the viral sequence for several years, and then reverted back to the B consensus form, RMYSPSTSI.

**HXB2 Location** p24 (143–150)  
**Author Location**

**Epitope** RMYSPSTSI

**Immunogen** HIV-1 infection, vaccine

**Vector/Type:** canarypox, canarypox prime with recombinant protein boost **Strain:** B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen **HIV component:** Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B52)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p24 (143–151)  
**Author Location** p24 (143–151)

**Epitope** RMYSPVSIL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope RMYSPVSIL is highly conserved across clades with >80% conservation to subtypes A, C and D.

**HXB2 Location** p24 (143–151)  
**Author Location** Gag (275–283)

**Epitope** RMYSPSTSI

**Subtype** B

**Immunogen** vaccine

**Vector/Type:** lipopeptide **Strain:** B clade LAI **HIV component:** Env, Gag, Nef **Adjuvant:** QS21

**Species (MHC)** human (A2)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** p24 (143–151)

**Author Location** Gag (275–283 BRU)

**Epitope** RMYSPSTIL

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivorian subjects
- This epitope was recognized by 1/9 CRF02\_AG-infected Ivorians, and 0/9 B-infected French subjects.

**HXB2 Location** p24 (143–151)

**Author Location** Gag (275–283 HXB2)

**Epitope** RMYSPSTIL

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Viet Nam

**Assay type** HLA binding

**Keywords** subtype comparisons, computational epitope prediction, escape, variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- The most common CRF01\_AE variant rmyspVsil had a higher HLA-binding score than the HXB2 epitope. The rare variant, rmyspVsiW was predicted not to bind to A2.

**HXB2 Location** p24 (143–151)

**Author Location** Gag (Henan isolate)

**Epitope** RMYSPSTIL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p24 (144–151)

**Author Location** Gag (276–283)

**Epitope** MYSPTSIL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A24)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** p24 (149–158)

**Author Location** Gag

**Epitope** SILDIRQGPK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p24 (151–170)

**Author Location** p24 (283–302 SF2)

**Epitope** LDIRQGPKPFRDYVDRFYK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** McAdam *et al.* 1998

**HXB2 Location** p24 (152–162)  
**Author Location** p24 (152–162)  
**Epitope** DIRQGPKEPFR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*27)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, DIRQGPKEPFR, was detected within overlapping peptides SILDIRQGPKEPFRDYV and GPKEPFRDYVDRFYKTLR.

**HXB2 Location** p24 (156–173)  
**Author Location** Gag  
**Epitope** GPKEPFRDYVDRFYKTLR  
**Epitope name** GAG-40  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, immunodominance  
**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].

- This peptide, GPKEPFRDYVDRFYKTLR differs from the consensus C sequence GPKEPFRDYVDRFfKTLR at 1 amino acid position, i.e. by 5.6%.

**HXB2 Location** p24 (156–173)  
**Author Location** p24  
**Epitope** GPKEPFRDYVDRFYKTLR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, GPKEPFRDYVDRFYKTLR, had an overall frequency of recognition of 16.7% - 18.6% AA, 11.5% C, 15.9% H, 14.3% WI. This peptide is included in a 43 aa Gag-p24 highly reactive region to be used for vaccine design.

**HXB2 Location** p24 (157–178)  
**Author Location** p24 (290–309)  
**Epitope** PKEPFRDYVDRFYKTLRAEQAS  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**References** Musey *et al.* 1997

- Cervical and peripheral blood derived CTL clones from an HIV-infected woman recognized this epitope.

**HXB2 Location** p24 (159–168)  
**Author Location** p24 (159–168)  
**Epitope** EPFRDYVDRF

- Subtype C**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, immunodominance  
**References** Thakar *et al.* 2005
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
  - 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
  - 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
  - Epitope EPFRDYVDRF was highly conserved across all clades at >80%.
- HXB2 Location** p24 (159–168)  
**Author Location** Gag (291–300)  
**Epitope** EPFRDYVDRF  
**Immunogen** vaccine  
*Vector/Type:* DNA, DNA with protein boost  
*Strain:* B clade LAI *HIV component:* Gag, Nef, Tat *Adjuvant:* IL-18  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Keywords** Th1  
**References** Billaut-Mulot *et al.* 2001
- DNA vaccinated BALB/c mice primed and boosted with the multiepitopic vaccine with IL18 showed lymphoproliferative responses 7 weeks post immunization.
  - Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime/DNA boost was more effective than DNA prime protein boost.
  - Immunization with either the multiepitopic DNA or with the mixed DNA vaccine induced HIV-1 specific Th1 cytokines (IL-2 and IFN- $\gamma$ )
  - Co-administration of IL18 increased T-cell responses but decreased anti-HIV antibody levels.
- HXB2 Location** p24 (159–168)  
**Author Location** p24  
**Epitope** EPFRDYVDRF  
**Epitope name** E10F  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Gag  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Assay type** Chromium-release assay  
**References** Bojak *et al.* 2002b
- Codon-optimized gag gene DNA vaccines were compared to wild type by vaccination of BALB/c mice. Codon optimized DNA gave a Th1 polarized Th response, a strong antibody response that persisted from more than 20 weeks, and CTL responses, while wild-type DNA induced weak and inconsistent immune responses.

- HXB2 Location** p24 (159–168)  
**Author Location**  
**Epitope** EPFRDYVDRF  
**Epitope name** E10F  
**Immunogen** vaccine  
*Vector/Type:* DNA, virus-like particle (VLP), polypeptide *HIV component:* Gag, p24 Gag, V3  
**Species (MHC)** mouse (H-2L<sup>d</sup>)  
**Assay type** Cytokine production, Chromium-release assay  
**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance  
**References** Wild *et al.* 2004
- A codon optimized gag DNA vaccine was compared to a myristylation defective gag and p24 alone, both of which lack signals for secretion from transfected cells. Gag-derived immunogens that were secreted as VLPs and those that remained intracellular (p24) each produced strong CTL responses, and neither the size of antigen nor cellular trafficking and localization significantly influenced the strength of humoral and cellular immune activation. The formation and release of VLPs was not essential for eliciting strong CTL. BALB/c mice were given the DNA vaccine by i.m. administration of plasmid DNA for the prime and boost.
  - Minigenes were made incorporating just 1 epitope, minitopes, carrying 1 of 3 murine class I epitopes linked to the Ad2-E3 protein-derived signal peptide to allow access of the epitope to the ER. Weak induction of cellular immune responses was observed, in contrast to the complex polyprotein. The E10F minigene did not produce a detectable CTL response.
- HXB2 Location** p24 (159–168)  
**Author Location** p24 (287–309)  
**Epitope** EPFRDYVDRF  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* p24 Gag  
**Species (MHC)** mouse  
**References** Nakamura *et al.* 1997
- Mice immunized with this synthetic peptide generated specific CTLs, a proliferative response, and antibodies.
  - The amino acids shown in the epitope field were based on the numbering provided by Nakamura *et al.*, and may not be correct.
  - The CTL epitope was located in position 291-300.
- HXB2 Location** p24 (159–168)  
**Author Location** Gag (291–300)  
**Epitope** EPFRDYVDRF  
**Subtype** B  
**Immunogen** HIV-1 infection, peptide-HLA interaction  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** immunodominance  
**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, EPFRDYVDRF, is similar to human protein COPINE 5, sequence vPFRDYVDR.

**HXB2 Location** p24 (159–169)

**Author Location** Gag (292–301)

**Epitope** EPFRDYVDRFF

**Subtype** A, C, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*81)

**Country** Tanzania

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, immunodominance

**References** Geldmacher *et al.* 2007a

- To assess whether T-cell specific responses to Gag and Nef are biased towards infecting subtype recombination, 56 ART-naive subjects were studied using six overlapping peptide sets consisting 15-mer peptides, covering both proteins completely. A multi-region hybridization assay was employed. Overall, the best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants EPFRDYVDRFf and EPFRDYVDRFy were studied as peptide sequences PK-EPFRDYVDRFf-KT (subtypes C and A) and PK-EPFRDYVDRFy-KT (subtype D) with 12.5% responders. Subtypes C and A were best recognized.

**HXB2 Location** p24 (159–178)

**Author Location** Gag (96ZM651.8)

**Epitope** EPFRDYVDRFFKTLRAEQAT

**Immunogen**

**Species (MHC)** human (B\*440301)

**Keywords** subtype comparisons, immunodominance

**References** Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 16 of 46 (34.8%) had CTL responses to one or more peptides within the second immunodominant region region of Gag (peptides SILDIKQGPKPEFRDYVDRF, EPFRDYVDRFFKTLRAEQAT, and FKTLRAEQATQEVKNWMTDT) with ELISPOT results median and range 500 (100 to 1,250) SFC/10<sup>6</sup> PBMC

- 3 of 6 (50%) carriers of HLA-B\*44031 showed CTL responses to the peptide EPFRDYVDRFFKTLRAEQAT.

**HXB2 Location** p24 (159–178)

**Author Location** Gag (291–310)

**Epitope** EPFRDYVDRFFKTLRAEQAT

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** p24 (160–169)

**Author Location** p24

**Epitope** PFRDYVDRFF

**Epitope name** PF-10

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA

**References** Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. This is 1 of 5 novel epitopes that were found among subtype C HIV-1 from African patients who hadn't previously been identified in B clade infections. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles. The HLA restricting element for this optimal epitope was not determined due to limited material.

**HXB2 Location** p24 (161–169)

**Author Location**

**Epitope** FRDYVDRFF

**Immunogen**

**Species (MHC)** human (Cw\*18)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an Cw18 epitope.

**HXB2 Location** p24 (161–169)

**Author Location** (C consensus)

**Epitope** FRDYVDRFF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*1801)

**Country** South Africa



- Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004
- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
  - This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.
- HXB2 Location** p24 (161–169)  
**Author Location** (C consensus)  
**Epitope** FRDYVDRFF  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*1801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - FRDYVDRFF is an optimal epitope.
- HXB2 Location** p24 (161–169)  
**Author Location** p24 (161–169)  
**Epitope** FRDYVDRFF  
**Immunogen** peptide-HLA interaction  
**Species (MHC)** human (Cw\*1801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** optimal epitope  
**References** Honeyborne *et al.* 2006
- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B\*3910, B\*4201, B\*8101 and Cw\*1801, by motif inference. HLA-A\*2902 was found to overlap those of A1 and A24 supertypes.
  - FRDYVDRFF was the optimal epitope for HLA-Cw\*1801 with variants FRDYVDRF, RDYVDRFF, FRDYVDRFFk, pFRDYVDRFF having been tested.
- HXB2 Location** p24 (161–170)  
**Author Location** p24 (subtype B, D)  
**Epitope** FRDYVDRFYK  
**Subtype** B, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1801)  
**References** Ogg *et al.* 1998a
- Noted in Brander 1999, this database, to be B\*1801, FRDYVDRFY.
- HXB2 Location** p24 (161–170)  
**Author Location** p24 (subtype B, D)  
**Epitope** FRDYVDRFYK  
**Subtype** B, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is a B\*1801 epitope.
- HXB2 Location** p24 (161–170)  
**Author Location** p24 (161–170 HXB2)  
**Epitope** FRDYVDRFYK  
**Epitope name** FK10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1801)  
**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape, immune evasion, optimal epitope  
**References** Liu *et al.* 2006b
- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- HXB2 Location** p24 (161–170)  
**Author Location** p24 (161–170)  
**Epitope** FRDYVDRFYK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B18)  
**References** Ferrari *et al.* 2000
- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.
- HXB2 Location** p24 (161–170)  
**Author Location** p24 (293–302)  
**Epitope** FRDYVDRFYK  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (B18)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2001a
- Variants FRDYVDRF(Y/F)K are specific for the B,D/A,C clades.
  - ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B18 women, 3/4 HEPS and 1/9 HIV-1 infected women recognized this epitope, likelihood ratio 5.3, p value 0.04, and HEPS women tended to respond to FRDYVDRFY/FK, while infected women tended to respond to YPLTFGWCY/F.
- The dominant response to this HLA allele was to this epitope for all 3/4 HEPS cases and for the single HIV-1 infected women that responded to this epitope.
- Four epitopes were considered to be “resistant epitopes”, as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILK(D/E)PVHGV in RT, A\*6802 DTVLEDINL in Protease, B14 DLNM/TLN(I/V)V in p24 and B18 FRDYVDRF(Y/F)K also in p24.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A\*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.

**HXB2 Location** p24 (161–170)

**Author Location** p24

**Epitope** FRDYVDRFYK

**Subtype** B, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human, macaque (B18)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** p24 (161–170)

**Author Location** p24

**Epitope** FRDYVDRFYK

**Epitope name** B18-FK10(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (161–170)

**Author Location**

**Epitope** FRDYVDRFFK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML1732.

**HXB2 Location** p24 (161–174)

**Author Location** p24 (161–174 HXB2)

**Epitope** FRDYVDRFYKTLRA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

- HXB2 Location** p24 (161–175)  
**Author Location** p24 (161–170)  
**Epitope** FRDYVDRFYKTLRAE  
**Subtype** A, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*0101, A\*7401, B\*5801  
**Country** Uganda  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization  
**References** Barugahare *et al.* 2005
- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
  - The sequence contains a known epitope (FRDYVDRFYKTL), but the subject recognizing it does not carry HLAs of the previously-defined restriction. The isolated viral sequence was frdyvdrfykVlrae, from the patient that could recognize the peptide.

**HXB2 Location** p24 (161–180)  
**Author Location** p24 (293–312 SF2)  
**Epitope** FRDYVDRFYKTLRAEQASQD  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B71)  
**References** McAdam *et al.* 1998

**HXB2 Location** p24 (161–180)  
**Author Location** p24 (293–312 SF2)  
**Epitope** FRDYVDRFYKTLRAEQASQD  
**Immunogen** HIV-1 infection  
**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A2, A3, B8, B62.

**HXB2 Location** p24 (161–180)  
**Author Location** p24 (293–312 SF2)  
**Epitope** FRDYVDRFYKTLRAEQASQD  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** p24 (162–172)  
**Author Location** p24 (296–306 subtype A)  
**Epitope** RDYVDRFFKTL  
**Subtype** A  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2402)  
**Keywords** subtype comparisons  
**References** Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa.
- This epitope is similar to the A24 DYVDRYFKT epitope found for B subtype, but CTL from this A subtype infection required the additional Arg – the B clade sequence change from F to Y diminished CTL reactivity.
- C. Brander notes that this is an A\*2402 epitope in the 1999 database.

**HXB2 Location** p24 (162–172)  
**Author Location** p24 (296–306 subtype A)  
**Epitope** RDYVDRFFKTL  
**Subtype** A  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2402)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*2402 epitope.

**HXB2 Location** p24 (162–172)  
**Author Location** p24 (296–306)  
**Epitope** RDYVDRFFKTL  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (A24)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A24 women, 0/4 HEPS and 6/10 HIV-1 infected women recognized this epitope, likelihood ratio 7.2, p value 0.03, and (R)YL(R/K)DQQLL tended to be reactive in HEPS and infected women, RDYVDRFFKTL in infected women only.
- The dominant response to this HLA allele was to this epitope in all of the 6/10 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A\*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Subject ML 1707 started with a CTL response to A\*6802 DTVLEDINL prior to seroconversion, and switched to A\*6802 ETAYFILKL and A24 RDYVDRFFKTL post-seroconversion.

**HXB2 Location** p24 (162–172)

**Author Location** p24

**Epitope** RDYVDRFFKTL

**Epitope name** A24-RL11(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (162–172)

**Author Location** p24 (293–312 LAI)

**Epitope** RDYVDRFYKTL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4402)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*4402 epitope.

**HXB2 Location** p24 (162–172)

**Author Location** p24 (162–172)

**Epitope** RDYVDRFYKTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (162–172)

**Author Location** p24 (162–172)

**Epitope** RDYVDRFYKTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**References** Day *et al.* 2001

**HXB2 Location** p24 (162–172)

**Author Location** p24

**Epitope** RDYVDRFYKTL

**Subtype** B, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade HIV component: p17 Gag, p24 Gag

**Species (MHC)** human, macaque (B44)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** p24 (162–172)

**Author Location** Gag (B con)

**Epitope** RDYVDRFYKTL

**Epitope name** RL11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** variant cross-recognition or cross-neutralization

**References** Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN ELISPOT responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the ELISPOT assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
- 1 subject recognized this epitope with low functional avidity. The autologous sequence matched the B consensus.

**HXB2 Location** p24 (162–172)

**Author Location** p24

**Epitope** RDYVDRFYKTL

**Epitope name** B44-RL11(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Assay type** CD8 T-cell ELISPOT - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (162–172)

**Author Location** p24 (293–312 LAI)

**Epitope** RDYVDRFYKTL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A26, B44, B70)

**References** Ogg *et al.* 1998a

**HXB2 Location** p24 (163–173)

**Author Location** Gag (295–303 SUMA)

**Epitope** DYVDRFYKT

**Epitope name** Gag DT9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell ELISPOT - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** p24 (163–172)

**Author Location** p24 (163–172)

**Epitope** DYVDRFYKTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (163–173)

**Author Location** Gag (297–307 SF2)

**Epitope** DYVDRFYKTLR

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (A\*3303)

**Assay type** Chromium-release assay

**Keywords** binding affinity, computational epitope prediction

**References** Hossain *et al.* 2003

- HLA-A\*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A\*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A\*3303. Six of these served as peptide-targets for lysis by PBMC from infected individual, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
- This epitope is one of the 2/6 peptides that could induce CTL responses in the PBMC of infected individuals, but was not properly processed in a vaccinia-HIV infected target cell.

**HXB2 Location** p24 (164–172)  
**Author Location** p24 (164–172)  
**Epitope** YVDRFYKTL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, YVDRFYKTL, was detected within overlapping peptides SILDIRQGPKPEFRDYV and GPKEPFRDYV-DRFYKTLR.

**HXB2 Location** p24 (164–172)  
**Author Location** Gag (296–304)  
**Epitope** YVDRFYKTL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0207)  
**Donor MHC** A\*0207  
**Keywords** subtype comparisons  
**References** Currier *et al.* 2002a

- Cross-reactive responses were found in PBMC isolated from individuals infected with either B or CRF01\_AE clade viruses, as determined by Elispot assays of target cells expressing recombinant vaccinia viruses expressing HIV-1 gag, env, nef and pol from many clades.
- The Thai subject VAIP-4 demonstrated broad CTL cross-reactivity towards gag constructs derived from subtypes A, B, C, D, F, G, H, and CRF-01\_AE. Sequence alignments of this epitope showed conservation for clades B and D, and Y->F substitutions at position 6 for subtypes A, C, CDR01-AE, F, G, and H. YVDRFYKTL and the variant epitope YVDRFFKTL are recognized equally well.

**HXB2 Location** p24 (164–172)  
**Author Location** p24 (164–172)  
**Epitope** YVDRFYKTL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0207)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** p24 (164–172)  
**Author Location** p24 (164–172)  
**Epitope** YVDRFFKTL

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2601)  
**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding  
**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism  
**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, YVDRFFKTL, was predicted to be restricted by HLA A\*0203, A\*0204, A\*0207, A\*2601 and B\*3801.

**HXB2 Location** p24 (164–172)  
**Author Location** p24  
**Epitope** YVDRFYKTL  
**Epitope name** A2-YL9(p24)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (164–172)  
**Author Location** p24 (298–306 subtype A)  
**Epitope** YVDRFFKTL  
**Subtype** A  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A26, B70)  
**Keywords** subtype comparisons  
**References** Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa.
- This CTL epitope is conserved in A and C subtype, and B clade sequences tend to have a change from F to Y, YVDRFYKTL – both variants showed strong CTL reactivity.
- CTL reacted with targets presenting either in the context A26 or B70 – the epitope has the HLA-26 motif of Val at position 2 and Leu at the carboxy terminus, and the B70 anchor residue motif is unknown.

**HXB2 Location** p24 (164–172)

**Author Location** Gag (298–306 subtype A)

**Epitope** YVDRFFKTL

**Subtype** A

**Immunogen** HIV-1 infection, in vitro stimulation or selection

**Species (MHC)** human (A26, B70)

**Keywords** subtype comparisons

**References** Dorrell *et al.* 2001

- In vitro restimulation of CTL specific for dominant epitopes from infected individuals is possible using recombinant modified vaccinia virus Ankara (MVA) carrying A or D subtype HIV-1 Gag proteins.

**HXB2 Location** p24 (164–172)

**Author Location** p24

**Epitope** YVDRFFKTL

**Epitope name** YL-9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA

**References** Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized.
- YVDRFFKTL was presented by B\*15, which is more common in Zulus than Caucasians (0.153 versus 0.079). This epitope had previously identified in B clade infections.

**HXB2 Location** p24 (164–172)

**Author Location**

**Epitope** YVDRFFKTL

**Immunogen**

**Species (MHC)** human (B\*1503)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B\*1503 epitope.

**HXB2 Location** p24 (164–172)

**Author Location** Gag (296–304)

**Epitope** YVDRFFKTL

**Subtype** A, C, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1510)

**Country** Tanzania

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, immunodominance

**References** Geldmacher *et al.* 2007a

- To assess whether T-cell specific responses to Gag and Nef are biased towards infecting subtype recombination, 56 ART-naive subjects were studied using six overlapping peptide sets consisting 15-mer peptides, covering both proteins completely. A multi-region hybridization assay was employed. Overall, the best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.
- Epitope variants YVDRFfKTL and YVDRFyKTL (HLA-B\*1503) were studied as peptide sequences FRD-YVDRFfKTL-RAE (subtypes C and A) and FRD-YVDRFyKTL-RAE (subtype D), with 30% responders. Subtypes C and A epitopes were best recognized.

**HXB2 Location** p24 (164–172)

**Author Location** Gag (296–304 96ZM651.8)

**Epitope** YVDRFFKRL

**Immunogen**

**Species (MHC)** human (B\*1510, B70)

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 4 subjects who responded to the CTL epitope YVDRFFKTL – all were HLA-B\*1510 and also shared HLA-Cw03, suggesting linkage disequilibrium.
- An HIV-1 B variant of the epitope YVDRFYKTL has been described, and was recognized by CTL from an HIV-1 subtype A-infected patient, and the HLA restriction of the epitope was suggested to be A26 or B70 – HLA-B\*1510 is equivalent to the serological specificity HLA B70.

**HXB2 Location** p24 (164–172)

**Author Location** p24

**Epitope** YVDRFFKTL

**Epitope name** B15-YL9(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (164–172)

**Author Location** p24 (164–172)

**Epitope** YVDRFYKTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B70)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (164–172)

**Author Location** p24 (164–172)

**Epitope** YVDRFFKTL

**Immunogen**

**Species (MHC)** human (Cw\*0303)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** p24 (164–172)

**Author Location** p24 (164–172)

**Epitope** YVDRFFKTL

**Immunogen**

**Species (MHC)** human (Cw\*0304)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** p24 (164–172)

**Author Location** (C consensus)

**Epitope** YVDRFFKTL

**Epitope name** YL9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0304)

**Donor MHC** A\*3402, B\*0801, B\*4403, Cw\*0304, Cw\*0401

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was one of two used to illustrate how specific epitopes were characterized with regard to defining the optimal epitope and the HLA restricting element. HLA allelic associations in the population with peptide recognition was highly predictive of the epitope within the 15 mer.

**HXB2 Location** p24 (164–172)

**Author Location** (C consensus)

**Epitope** YVDRFFKTL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0304)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the T8 residue of YVDRFFKTL are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** p24 (164–172)

**Author Location** p24

**Epitope** YVDRFFKTL

**Epitope name** YL9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0304)

**Country** South Africa

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization

**Keywords** rate of progression

**References** Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naïve patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer Cw\*0304 YL9 was used to test 24 patients and gave a median ex vivo tetramer frequency of 2.26.

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**HXB2 Location** p24 (164–172)

**Author Location** Gag

**Epitope** YVDRFFKTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0304)

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization

**References** Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRFFKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- This immunodominant sequence FRDYVDRFFKTLRAE is associated with HLA-Cw\*0304 and contains the minimal epitope YVDRFFKTL.

**HXB2 Location** p24 (164–172)

**Author Location**

**Epitope** YVDRFFKTL

**Epitope name** YL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0304)

**Country** South Africa

**Assay type** proliferation, Tetramer binding, Intracellular cytokine staining

**References** Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

**HXB2 Location** p24 (164–172)

**Author Location**

**Epitope** YVDRFFKTL?

**Epitope name** YL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw0304)

**Country** United States, South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** memory cells

**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated

impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** p24 (164–181)

**Author Location** Gag

**Epitope** YVDRFYKTLRAEQASQEV

**Epitope name** GAG-41

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, YVDRFYKTLRAEQASQeV differs from the consensus C sequence YVDRFfKTLRAEQAtQdV at 3 amino acid positions, i.e. by 16.7%.

**HXB2 Location** p24 (164–181)

**Author Location** p24

**Epitope** YVDRFYKTLRAEQASQEV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but

the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.

- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. *J. Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, YVDRFYKTLRAEQASQEV, had an overall frequency of recognition of 25.3% - 22% AA, 30.8% C, 31.8% H, 14.3% WI. This peptide is included in a 43 aa Gag-p24 highly reactive region to be used for vaccine design.

**HXB2 Location** p24 (164–181)

**Author Location** Gag (298–315)

**Epitope** YVDRFYKSLRAEQTDPVAV

**Subtype** HIV-2

**Immunogen** HIV-2 infection

**Species (MHC)** human

**Country** Guinea-Bissau

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** rate of progression, optimal epitope, HIV-2

**References** Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.
- This peptide, YVDRFYKSLRAEQTDPVAV, was most frequently recognized at 20 out of 65 different subjects. Its responses can be both CD8 and CD4 T cell restricted.

**HXB2 Location** p24 (165–178)

**Author Location** p24 (165–178)

**Epitope** VDRFYKTLRAEQAS

**Epitope name** VS14

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*33 motif)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, subtype comparisons, acute/early infection

**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this epitope, VS14 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen to both A- and C-clade variants. An anchor residue is at position 9; while both A- and C- variants contain a change at position 14 to VDRFYKTLRAEQAT.

**HXB2 Location** p24 (165–178)

**Author Location** p24 (165–177 HXB2)

**Epitope** VDRFYKTLRAEQAS

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p24 (165–179)

**Author Location****Epitope** VDRFYKTLRAEQASQ**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A3, A32; B38, B64**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** vaccine-induced epitopes**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was recognized by a placebo patient after infection.

**HXB2 Location** p24 (165–184)**Author Location** Gag (297–311)**Epitope** VDRFYKTLRAEQASQ**Epitope name** VQ15**Immunogen** HIV-1 infection**Species (MHC)** human (B\*57)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- One subject responded to peptide VQ15, a non-B\*57-restricted peptide.

**HXB2 Location** p24 (166–174)**Author Location** p24 (166–174)**Epitope** DRFYKLTRA**Epitope name** DA9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*14)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** binding affinity, subtype comparisons, acute/early infection**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this epitope, DA9 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen to both A- and C-clade variants. An anchor residue is at position 2; while both A- and C- variants contain a change at position 4 to DRFFKLTRA.

**HXB2 Location** p24 (166–174)**Author Location** (C consensus)**Epitope** DRFFKTLRA**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*1401)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- DRFFKTLRA is an optimal epitope.

**HXB2 Location** p24 (166–174)**Author Location** p24 (298–306 LAI)**Epitope** DRFYKTLRA**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*1402)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1402 epitope.

**HXB2 Location** p24 (166–174)**Author Location** (167–175)**Epitope** DRFFKTLRA**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*1402)**Assay type** Other**Keywords** HLA associated polymorphism**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases

and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.

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- DRFFKTLRA was a previously defined B\*1402 presented epitope that encompassed a B\*14/B\*1401 associated polymorphism, DRFFKTLRA, in the fifth position. This epitope is embedded in a previously determined CTL immunodominant region.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (166–174)

**Epitope** DRFFKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1402)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naïve individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naïve T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, DRFFKTLRA, was predicted to be restricted by HLA B\*1402, B\*2701, B\*2702, B\*2703, B\*2704, B\*2705 and B\*2709.

**HXB2 Location** p24 (166–174)

**Author Location** p24

**Epitope** DRFFKTLRA

**Epitope name** DA-9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1403)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA

**References** Masemola *et al.* 2004b

- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized.
- DRFFKTLRA was presented by B\*14, which is more common in Zulus than Caucasians (0.066 versus 0.038). This epitope had previously identified in B clade infections.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (298–306 IIIB)

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** responses in children, mother-to-infant transmission

**References** Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- DRFYKTLRA, a naturally occurring variant, was found in mother, and is recognized although less reactive.
- DQFYKTLRA, a naturally occurring variant, was found in infant and is not recognized.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (298–306 IIIB)

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Cao *et al.* 1997a

- The consensus peptide for clades B and D is DRFYKTLRA.
- The consensus peptide for clades A and C is DRFFKTLRA and it is equally reactive.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (298–306 HXB2)

**Epitope** DRFYKTLRA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** kinetics

**References** Yang *et al.* 1997b

- A chimeric universal T cell receptor was created by linking CD4 or an HIV-specific anti-gp41 Ig sequence to the signaling domain of the T cell receptor chain  $\zeta$ , and transducing into CD8+ cells.
- The response using universal-receptor-bearing CD8+ cells to lyse infected cells *in vitro* was comparable to the natural occurring responses of CTL-clones from HIV+ individuals in terms of kinetics and efficiency.

- A CTL clone specific for this epitope was used for the comparison.

**HXB2 Location** p24 (166–174)

**Author Location** p24

**Epitope** DRFWKTLRA

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B14)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The D subtype consensus is identical to the B clade epitope.
- The A subtype consensus is drFfKtLRA.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (298–306 LAI)

**Epitope** DRFYKTLRA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Harrer *et al.* 1996b

**HXB2 Location** p24 (166–174)

**Author Location** p24 (298–306)

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Yang *et al.* 1996

- CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL.
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones.
- The distinction was thought to be due to lower expression of RT relative to Env and Gag.
- CTL can lyse infected cells early after infection, possibly prior to viral production.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (298–306)

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Assay type** CTL suppression of replication

**References** Yang *et al.* 1997a

- CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*.
- CTL produced HIV-1-suppressive soluble factors – MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, after antigen-specific activation.
- CTL suppress HIV replication more efficiently in HLA-matched cells.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (298–306)

**Epitope** DRFYKTLRA

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (B14)

**Keywords** dendritic cells

**References** Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYKTLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPVKVQWPL.

**HXB2 Location** p24 (166–174)

**Author Location** p24

**Epitope** DRFYKLTRA

**Immunogen**

**Species (MHC)** human (B14)

**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: DRFYKSLRA is cross-reactive, Harrer *et al.* [1993]

**HXB2 Location** p24 (166–174)

**Author Location** p24 (298–306 IIIB)

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- DRFYKILRA and DQFYKTLRA were escape mutants.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (SF2)

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in 2/5 HIV+ individuals who were HLA B14 living in Boston – this epitope did not fall within the three most recognized peptides in the study.

- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLG (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (SF2)

**Epitope** DRFYKTLRA

**Epitope name** DA9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** acute/early infection

**References** Goulder *et al.* 2001a

- Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia.
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (166–174)

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (298–306 SF2)

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B14+ individuals that had a CTL response to this epitope broken down by group: 3/3 group 1, 1/2 group 2, and 0/0 group 3.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (298–306)

**Epitope** DRFFKTLRA

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B14)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- Variants DRF(F/W)KTLRA are specific for clades A/B.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B14 women, 0/4 HEPS and 6/7 HIV-1 infected women recognized this epitope, likelihood ratio 14.4, p value 0.004 and HEPS women tended to respond to DLNMMMLNIV/DLNTMLNVV, while infected women tended to respond to DRF(F/W)KTLRA.
- The dominant response to this HLA allele was to this epitope for all of the 6/7 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A\*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (SF2)

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.

**HXB2 Location** p24 (166–174)

**Author Location** p24

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** epitope processing

**References** Cao *et al.* 2002

- AC13 is a B14 restricted CTL clone that recognizes DRFYKTLRA.
- CTL could be activated by a fusion protein of an HIV protein and anthrax lethal factor (LFn-HIV) that promotes antigen presenting cell uptake of exogenous protein and allows processing through the MHC class I pathway. This strategy for CTL detection could allow antigen presentation without generation of cells by the standard methods of using live viral

vectors carrying a protein, or by loading the cells with peptides and by-passing processing.

- HXB2 Location** p24 (166–174)  
**Author Location** p24  
**Epitope** DRFWKTLRA  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2002
- Neisseria gonorrhoea cervicitis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
  - Ghonorrhoea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

- HXB2 Location** p24 (166–174)  
**Author Location** p24  
**Epitope** DRFYKTLRA  
**Subtype** B, D  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade HIV component: p17 Gag, p24 Gag  
**Species (MHC)** human (B14)  
**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance  
**References** Hanke & McMichael 2000; Wee *et al.* 2002
- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
  - Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN-gamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

- HXB2 Location** p24 (166–174)  
**Author Location** p24 (166–174)  
**Epitope** DRFYKTLRA  
**Subtype** B  
**Immunogen** HIV-1 infection

- Species (MHC)** human (B14)  
**Donor MHC** A1, A3, B14, B7, Cw\*0702, Cw\*0802; A1A1, B14, B8, Cw7, Cw8  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** acute/early infection, early-expressed proteins

- References** Cao *et al.* 2003
- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
  - This epitope was recognized in two subjects early in infection, presented by B14 in each case.
  - All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
  - More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

- HXB2 Location** p24 (166–174)  
**Author Location** p24 (166–174)  
**Epitope** DRFYKTLRA  
**Epitope name** Gag/p24-DA9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Assay type** Chromium-release assay  
**Keywords** binding affinity, TCR usage, characterizing CD8+ T cells  
**References** Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 1/14 CTL T-cell clones tested were specific for Gag/p24-DA9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 value for Gag/p24-DA9 was 100,000 pg/ml, it had the lowest avidity of the 14 tested.

- HXB2 Location** p24 (166–174)

**Author Location** (C consensus)**Epitope** DRFFKTLRA**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B14)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** characterizing CD8+ T cells**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (166–174)**Author Location** (B consensus)**Epitope** DRFYKTLRA**Epitope name** DA9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B14)**Donor MHC** A28, A29, B14, B44, Cw8; A25, A32, B08, B14, Cw7, Cw8; A03, B14, B60, Cw3, Cw7**Country** United States**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 3/9 individuals recognized this epitope, presented by HLA-B14.

**HXB2 Location** p24 (166–174)**Author Location** Gag (298–306)**Epitope** DRFYKTLRA**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B14)**Donor MHC** A28, A29, B14, B44, Cw8**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** p24 (166–174)**Author Location** Gag (298–306)**Epitope** DRFYKTLRA**Epitope name** DA9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B14)**Donor MHC** A\*02, A\*68, B\*14, B\*52, Cw\*08, Cw\*12**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** escape, optimal epitope**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- A form of this epitope that elicited a diminished Elispot response, DRFYrTLRA, dominated the viral sequence for several years, and then reverted back to the B consensus form, DRFYKTLRA.

**HXB2 Location** p24 (166–174)**Author Location** p24**Epitope** DRFYKTLRA**Epitope name** DA9**Immunogen****Species (MHC)** (B14)**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion**References** Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** p24 (166–174)**Author Location** p24**Epitope** DRFYKTLRA**Epitope name** B14-DA9(p24)**Immunogen** HIV-1 infection**Species (MHC)** human (B14)**Assay type** CD8 T-cell Elispot - IFN $\gamma$



**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (166–174)

**Author Location**

**Epitope** DRFYKTLRA

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B14)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p24 (166–174)

**Author Location** p24 (subtype B)

**Epitope** DRFYKTLRA

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B\*1402, B14)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.

- The Clade A version of the epitope, DRFFKLTRA, was preferentially recognized by CTL.
- This epitope was recognized by two different exposed and uninfected prostitutes.

**HXB2 Location** p24 (166–175)

**Author Location** p24 (298–306 HX10)

**Epitope** DRFYKTLRAE

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** immunodominance

**References** Wagner *et al.* 1999

- The immunodominant CTL response in a long-term survivor was to this highly conserved and functionally relevant epitope.
- By testing mutations in an HXB2 background, it was found that all mutations within the epitope that abrogated CTL recognition also abolished viral infectivity.
- The epitope in this study overlaps the major homology region for which highly conserved residues exist in all known lentiviral and onco-viruses and yeast transposons.
- Patient was part of the study in Harrer *et al.* [1996a]

**HXB2 Location** p24 (166–175)

**Author Location** Gag (298–307)

**Epitope** DRFYKTRAE

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Donor MHC** A24, A33, B14, B27

**Assay type** Chromium-release assay

**Keywords** TCR usage, genital and mucosal immunity

**References** Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCR $\beta$  VDJ region sequencing revealed cases of expansion of the same clone in different compartments.
- CD8+ T cell clones directed at this epitope were derived from blood and cervix.

**HXB2 Location** p24 (166–176)

**Author Location** Gag (295–305 BORI)

**Epitope** DRFYKTLRAEQ

**Epitope name** Gag DQ11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1402)

**Donor MHC** A\*2902, B\*1402, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, immunodominance, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- DRFYKTLRAEQ didn't vary. There was no response in acute infection to this epitope, but the response was detectable by early infection.

**HXB2 Location** p24 (169–185)  
**Author Location** p24 (169–184 HXB2)  
**Epitope** YKTLRAEQASQDVKNWN  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** T-cell Elispot  
**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment  
**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- Responses to this peptide were detected in 17% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p24 (169–188)  
**Author Location** Gag (301–320)  
**Epitope** YKTLRAEQASQEVKNWMTET  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Donor MHC** A1, A66, B52, B57  
**Assay type** Chromium-release assay  
**Keywords** TCR usage, genital and mucosal immunity  
**References** Musey *et al.* 2003

- CTL clones from blood, semen, cervix and rectum samples from 12 individuals were compared. CTL clones derived from blood and mucosal samples had similar high lysis efficiency, primarily perforin dependent, and TCR $\beta$  VDJ region sequencing revealed cases of expansion of the same clone in different compartments.

- CD8+ T cell clones directed at this epitope were derived from blood and rectum.

**HXB2 Location** p24 (169–188)  
**Author Location** Gag (301–320)  
**Epitope** FKTLRAEQATQDVKNWMTDT  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons  
**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** p24 (171–180)  
**Author Location** p24  
**Epitope** TLRAEQATQD  
**Epitope name** TD-10  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*0304)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

- **Keywords** subtype comparisons, epitope processing, immunodominance, cross-presentation by different HLA

- References** Masemola *et al.* 2004b
- Highly targeted regions in Gag for CD8+ T-cells were defined for individuals with C clade infections in South Africa. 9 specific epitopes within the most reactive regions were characterized. This is 1 of 5 novel epitopes that were found among subtype C HIV-1 from African patients who hadn't previously been identified in B clade infections. Some epitopes were shown to be promiscuous, presented by multiple class I restricting alleles.
  - TLRAEQATQD was presented by Cw\*03 and newly identified in this study; Cw\*03 is more common in Zulus than Caucasians (0.157 versus 0.101).

**HXB2 Location** p24 (172–189)  
**Author Location** Gag  
**Epitope** LRAEQASQEVKNWMTETL  
**Epitope name** GAG-42  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, immunodominance  
**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, LRAEQAsQeVKNWMTeTL differs from the consensus C sequence LRAEQAtQdVKNWMTdTL at 3 amino acid positions, i.e. by 16.7%.

**HXB2 Location** p24 (172–189)

**Author Location** p24

**Epitope** LRAEQASQEVEKNWMTETL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, LRAEQASQEVEKNWMTETL, had an overall frequency of recognition of 22.7% - 20.3% AA, 46.2% C, 18.2% H, 9.5% WI. This peptide is included in a 43 aa Gag-p24 highly reactive region to be used for vaccine design.

**HXB2 Location** p24 (172–189)

**Author Location** Gag (306–323)

**Epitope** LRAEQTDPVKNWMTQTL

**Subtype** HIV-2

**Immunogen** HIV-2 infection

**Species (MHC)** human

**Country** Guinea-Bissau

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** rate of progression, optimal epitope, HIV-2

**References** Leligdowicz *et al.* 2007

- To find the factors involved in attenuated disease course and long term non-progression, HIV-2 and immune control were studied. HIV-2 viral load was used as a predictor of patient survival. HIV-2 viral load correlated inversely with magnitude of IFN-gamma response, relative dominance of Gag-specific peptides' responses over other proteins' responses, and the breadth of different peptide-specific immune responses. The most frequently recognized peptides were in Gag protein, followed by Env and Pol, while Nef and accessory proteins (Vif, Vpx, Vpr, Tat and Rev) rarely elicited responses. The 6 most recognized peptides were clustered in a highly conserved region of Gag.
- This peptide, LRAEQTDPVKNWMTQTL, was recognized by 11 out of 65 subjects. It is found in the 149 amino-acid long HIV-2 proteome region of Gag 175-323.

**HXB2 Location** p24 (173–181)

**Author Location** Gag (305–313 SUMA)

**Epitope** RAEQASQEV

**Epitope name** Gag RV9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0802)

**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single

patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.

- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** p24 (173–181)

**Author Location**

**Epitope** RAEQASQEV

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope RAEQASQEV elicited a magnitude of response of 220 SFC with a functional avidity of 0.01nM.

**HXB2 Location** p24 (173–181)

**Author Location** p24 (305–313)

**Epitope** RAEQASQEV

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**References** Johnson *et al.* 1991

- Originally reported as HLA-B14 restricted, but subsequently found not to be presented by cells transfected with B14.
- Thought to be HLA-Cw8 restricted (C. Brander and B. Walker)

**HXB2 Location** p24 (173–181)

**Author Location** p24

**Epitope** RAEQASQEV

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (Cw8)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.

- The A subtype consensus is RAEQAAtQEV.
- The D subtype consensus is RAEQsQdV.
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)

**HXB2 Location** p24 (173–181)

**Author Location** p24 (305–313)

**Epitope** RAEQASQEV

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**References** Price *et al.* 1995

- Study of cytokines released by HIV-1 specific activated CTL.
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)

**HXB2 Location** p24 (173–181)

**Author Location** p24 (305–313)

**Epitope** RAEQASQEV

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**References** Lubaki *et al.* 1997

- Eighty two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response.
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response.
- Despite this being a well defined conserved epitope, and thought to be presented by B14, none of the 11 gag-specific clones from a B-14 positive subject could recognize either it or p24 PQDLNTMLN.
- Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)

**HXB2 Location** p24 (173–181)

**Author Location** p24 (305–313)

**Epitope** RAEQASQEV

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (Cw8)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** p24 (173–181)

**Author Location** Gag (305–313)

**Epitope** RAEQASQEV

**Epitope name** RV9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**Donor MHC** A\*02, A\*68, B\*14, B\*52, Cw\*08, Cw\*12

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** escape, optimal epitope

**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences *in vivo*. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- Elispot responses to the consensus form of this epitope, RAEQASQEV, were much more intense than to the most common variants of the epitope found over time in this individual, RAEQASStEV and RAEQASQdV. There was a diminished response to RAEQASStEV and no response to RAEQASQdV, so these appear to be escape variants. The strong response to the consensus form persisted, despite the fact it was not observed among the autologous sequences until it surfaced as a minor variant (5/13 sequences) after 6 years of chronic infection.

**HXB2 Location** p24 (173–181)

**Author Location** p24

**Epitope** RAEQASQEV

**Epitope name** Cw8-RV9(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (173–181)

**Author Location**

**Epitope** RAEQASQEV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.

- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.

- This epitope was recognized in 1/22 HEPS sex worker controls ML1792.

**HXB2 Location** p24 (173–182)

**Author Location** Gag (Henan isolate)

**Epitope** RAEQASQEVK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p24 (173–183)

**Author Location** Gag (308–318)

**Epitope** RAEQATQDVKN

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p24 (174–184)

**Author Location** p24 (306–316 LAI)

**Epitope** AEQASQDVKNW

**Subtype** B

**Immunogen**

**Species (MHC)** human (B\*4402)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*4402 epitope.

**HXB2 Location** p24 (174–184)  
**Author Location** p24 (306–316 LAI)  
**Epitope** AEQASQDVKNW  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (B\*4402, B44)  
**References** Brander & Walker 1997  
 • Pers. comm. from D. Lewinsohn to C. Brander and B. Walker, C Brander *et al.*, this database, 1999.

**HXB2 Location** p24 (174–184)  
**Author Location** Gag (306–316)  
**Epitope** AEQASQEVKNW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**References** Brodie *et al.* 1999  
 • The ability of CTL effector cells was studied by expanding autologous HIV-1 Gag-specific CTL *in vitro*, and adoptively transferring them.  
 • The transferred CTLs migrated to the lymph nodes and transiently reduced circulating productively infected CD4+ T cells, showing that CTL move to appropriate target sites and mediate anti-viral effects.

**HXB2 Location** p24 (174–184)  
**Author Location** p24 (306–316)  
**Epitope** AEQASQEVKNW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**References** Brodie *et al.* 2000  
 • Study tracks and quantifies *in vivo* migration of neo-marked CD8 HIV-specific CTL.  
 • Adoptively transferred gene-marked HIV-specific CTL homed to specific lymph node sites, colocalizing within the parafollicular regions of the lymph node adjacent to cells expressing HIV tat-fusion transcripts, indicative of viral replication.  
 • The CTL clones expressed CCR5 and localized among HIV-1 infected cells expressing MIP-1alpha and MIP-1beta, CC-chemokines produced at sites of viral replication, suggesting a possible homing mechanism.  
 • This study provides a methodology for tracking and studying antigen specific CTL *in vivo*

**HXB2 Location** p24 (174–184)  
**Author Location** p24 (306–316 LAI)  
**Epitope** AEQASQDVKNW  
**Epitope name** G3  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Keywords** HAART, ART  
**References** Mollet *et al.* 2000  
 • A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFNgamma production to measure responses.

- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** p24 (174–184)  
**Author Location** p24 (174–184)  
**Epitope** AEQASQDVKNW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**References** Day *et al.* 2001  
 • B44-restricted CTL response was strongest to this epitope in one individual.

**HXB2 Location** p24 (174–184)  
**Author Location** p24  
**Epitope** AEQASQDVKNW  
**Epitope name** B44-AW11(p24)  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Donor MHC** A32, B44  
**Keywords** HAART, ART, supervised treatment interruptions (STI)  
**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient B displayed the greatest response to epitope B44-AW11(p24) and also responded to A32-PW10(RT) in both PB and LN samples, while a third response against epitope A32-RW10(gp120) was only detected in the LN sample.

**HXB2 Location** p24 (174–184)  
**Author Location** Gag (B con)  
**Epitope** AEQASQEVKNW  
**Epitope name** AW11

- Subtype B**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** variant cross-recognition or cross-neutralization  
**References** Draenert *et al.* 2004c
- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN Elispot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
  - 1 subject recognized this epitope with low functional avidity. The autologous sequence matched the B consensus.
- HXB2 Location** p24 (174–184)  
**Author Location** (B consensus)  
**Epitope** AEQASQDVKNW  
**Epitope name** AW11  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Donor MHC** A02, A11, B18, B44, Cw12, Cw5; A28, A29, B14, B44, Cw8  
**Country** United States  
**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells  
**References** Lichterfeld *et al.* 2004c
  - Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
  - 2/9 individuals recognized this epitope, presented by HLA-B44.

**HXB2 Location** p24 (174–184)  
**Author Location** Gag (306–316)  
**Epitope** AEQASQDVKNW  
**Epitope name** AW11  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Donor MHC** A11, A2, B18, B44, Cw12, Cw5  
**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay  
**Keywords** optimal epitope  
**References** Allen *et al.* 2005b

  - 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
  - This epitope did not vary.

**HXB2 Location** p24 (174–184)  
**Author Location** Gag (306–316)  
**Epitope** AEQASQDVKNW  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Donor MHC** A11, A2, B18, B44, Cw12, Cw5  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Allen *et al.* 2005a
  - Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** p24 (174–184)  
**Author Location** Gag (306–316)  
**Epitope** AEQASADVKNW  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Donor MHC** A28, A29, B14, B44, Cw8  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Allen *et al.* 2005a
  - Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** p24 (174–184)  
**Author Location** p24  
**Epitope** AEQASQDVKNW  
**Subtype** B, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Donor MHC** A23, A34, B44, B53, Cw4, Cw6  
**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype D Gag. The autologous epitope sequence had an D7E change, AEQASQeVKNW.

**HXB2 Location** p24 (174–184)

**Author Location** p24

**Epitope** AEQASQDVKNW

**Epitope name** B44-AW11(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (174–184)

**Author Location**

**Epitope** AEQASQDVKNW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.

- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope AEQASQDVKNW elicited a magnitude of response of 525 SFC with a functional avidity of 0.5nM.

**HXB2 Location** p24 (174–184)

**Author Location**

**Epitope** AEQASQDVKNW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B44), an additional HLA (B45) was statistically predicted to be associated with this epitope.

**HXB2 Location** p24 (174–185)

**Author Location** p24 (174–185)

**Epitope** AEQASQEVKNWM

**Immunogen**

**Species (MHC)** human (Cw5)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** p24 (175–186)

**Author Location** p24 (307–318)

**Epitope** EQASQEVKNWMT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**References** Quayle *et al.* 1998

- HIV is found in semen both as cell-associated and cell-free forms, and HIV-specific CTL could be found in the semen of 5/5 men with CD4 greater than 500 – 3 of the men were analyzed in detail and had broad CTL to gag, env and pol.
- Two CTL lines from one donor recognized this epitope.
- Isolation of CTLs specific to HIV in both male and female urinal tracts provide evidence that virus-specific lymphocytes come from the urogenital mucosa, and the authors speculate that CTL in mucosal tissues may be correlated with lower viral load in semen and reduced transmission.

**HXB2 Location** p24 (176–184)

**Author Location** p24 (308–316 LAI)

**Epitope** QASQEVKNW

**Subtype** B



- Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5301)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is a B\*5301 epitope.
- HXB2 Location** p24 (176–184)  
**Author Location** (C consensus)  
**Epitope** QATQDVKNW  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5301)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - QATQDVKNW is an optimal epitope.
- HXB2 Location** p24 (176–184)  
**Author Location**  
**Epitope** QASQEVKNW  
**Epitope name** Gag-QW9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5301, B57)  
**Donor MHC** 01RCH59: A\*0201, A\*3201, B\*4002, B\*5301, Cw\*0202, Cw\*0401  
**Keywords** HAART, ART  
**References** Sabbaj *et al.* 2003
- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
  - 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
  - Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
  - Subject 01RCH59 was Hispanic, was not on HAART, viral load 5100, CD4 count 349, and she also recognized PIKETWETW, RT(392-401), A\*3201.
  - Among HIV+ individuals who carried HLA B\*5301, 11/15 (73%) recognized this epitope.
  - Among HIV+ individuals who carried HLA B57, 3/6 (60%) recognized this epitope.
- HXB2 Location** p24 (176–184)  
**Author Location** Gag  
**Epitope** QASQEVKNW  
**Epitope name** QW9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape  
**References** Bailey *et al.* 2006b
- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
  - HLA-B\*57-restricted optimal epitope QASQEVKNW was tested for immune response.
- HXB2 Location** p24 (176–184)  
**Author Location** p24 (176–184)  
**Epitope** QASQEVKNW  
**Epitope name** QW10  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Country** United Kingdom, Kenya  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** TCR usage, structure, characterizing CD8+ T cells  
**References** Gillespie *et al.* 2006
- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.
  - In addition, immunodominancy of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFN-PEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.
- HXB2 Location** p24 (176–184)  
**Author Location** p24 (309–317 LAI)  
**Epitope** QASQEVKNW  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5701)  
**References** Goulder *et al.* 1996b
- Recognition of this peptide by two long-term non-progressors.
  - Peptide defined on the basis of B\*5801 binding motif, yet not cross-restricted except at high concentrations.
  - Described as B\*5701 in C. Brander *et al.*, this database, 1999.
- HXB2 Location** p24 (176–184)  
**Author Location** p24 (311–319 LAI)  
**Epitope** QASQEVKNW  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5701)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is a B\*5701 epitope.
- HXB2 Location** p24 (176–184)  
**Author Location**  
**Epitope** QASQEVKNW  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5701)  
**Keywords** rate of progression, immunodominance

**References** Migueles & Connors 2001

- HLA B\*5701 was found in a very high frequency in HIV-1 infected non-progressors, 11/13 (85%) versus 19/200 (9.5%) of progressors. Non-progressors tended to have an immune response that was highly focused on four p24 epitopes that were presented by B\*5701, ISPRTLNAW, KAFSPEVIPMF, TSTLQEIQGW, and QASQEVKNW.
- Only QASQEVKNW was recognized in all of the LTNP's tested.

**HXB2 Location** p24 (176–184)**Author Location****Epitope** QASQEVKNW**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701)**Keywords** rate of progression, immunodominance**References** Migueles & Connors 2001

- CTL activity was monitored in 27 individuals, including 10 LTNP with an over-expression of HLA B\*5701 – these individuals have viral loads below the threshold of infection without therapy, and their CD8+ T-cell response tends to be focused on peptides that contain B\*5701 epitopes ISPRTLNAW, KAFSPEVIPMF, TSTLQEIQGW, or QASQEVKNW.
- CTL responses are broader in B\*5701+ individuals with progressive viremia than those that control viremia.
- The HLA-A\*0201 SLYNTVATL epitope response was not as strong in individuals that carried both A2, B57.

**HXB2 Location** p24 (176–184)**Author Location** Gag (308–316)**Epitope** QASQEVKNW**Epitope name** QW9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701)**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay**Keywords** rate of progression, escape**References** Migueles *et al.* 2003

- cDNA Gag sequences from a set of 17 HLA-B\*5701+ progressors and 10 LTNPs were obtained, and the variation in four p24 B\*5701 epitopes examined. Sequence variants were more common ( $p < 0.01$ ) in the epitopes in the progressors (median 3, range 1-7) than LTNPs (median 2, range 0-4).
- In general use of the autologous protein in a target cell did not diminish the overall CD8+ T-cell responses.
- The substitution E312D (qasqDvknw) was common in progressors (8/17) and rare in LTNP (1/8) ( $p = 0.06$ ). qasqDvknw and qasqEvknw peptides were made; this mutation does not affect binding to B\*57. 2/4 progressors that carried only the D variant could not recognize the D variant peptide, but could recognize the E variant peptide, demonstrating immune escape.

**HXB2 Location** p24 (176–184)**Author Location** p24 (176–184)**Epitope** QASQEVKNW**Epitope name** QAS**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells**References** Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B57-QAS, that is very strongly associated with delayed progression to AIDS, and its alanine-substituted variants are weakly cross-recognized.

**HXB2 Location** p24 (176–184)**Author Location** (C consensus)**Epitope** QATQDVKNW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5801)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** characterizing CD8+ T cells**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (176–184)**Author Location** Gag (308–316)**Epitope** QASQEVKNW**Epitope name** QAS**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5801, B53)**Country** Gambia**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells, HIV-2**References** Gillespie *et al.* 2005

- CD8 T-cell responses were evaluated and compared in HIV-1 and HIV-2 infected individuals. A significantly greater magnitude and breadth of Gag-specific responses were found in HIV-1 infected individuals, possibly because undetectable viral load in HIV-2 infected individuals. This study suggests that responses in HIV-2 infection reflect antigen load in plasma, as is the case in HIV-1 infection. No correlation was found between immune control of HIV-2 and the frequency of perforin-expressing virus-specific CD8 T-cells.
- QASQEVKNW is a HIV-1 epitope cross-presented by B53 and B\*5801. It was recognized in 4/4 B\*5801+ HIV-1 infected individuals, and 7/7 B53+ HIV-1 infected individuals. HIV-2 infected individuals preferentially recognized the B58 HIV-2 epitope TSTVEEQIQW, and B53 epitope TPYDIN-QML.

**HXB2 Location** p24 (176–184)

**Author Location** p24 (308–316 LAI)

**Epitope** QASQEVKNW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**References** Buseyne *et al.* 1997

- Minimal sequence determined through epitope mapping.
- This is a relatively conserved epitope.
- HLA-Cw\*0401 was defined as the restricting element, but cells that carry Cw\*0401 varied in their ability to present this epitope – this could be the result of diminished cell-surface expression of Cw\*0401 in some cells.
- The HLA presenting molecule for this epitope was originally described as Cw\*0401, but subsequent experiments with an HLA B53+ C4- cell line and with C1R cells transfected with HLA-B53 have shown that the HLA restricting element is HLA-B53 (F. Buseyne, pers. comm. 2000)

**HXB2 Location** p24 (176–184)

**Author Location** p24 (NL43)

**Epitope** QASQEVKNW

**Epitope name** QW9

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (B53)

**Keywords** epitope processing, dendritic cells

**References** Buseyne *et al.* 2001

- Exogenous presentation or cross-presentation of epitopes by antigen presenting cells (APC) without protein synthesis is an alternative pathway for CTL epitope processing that may be important in the initial generation of viral specific CTL.
- Dendritic cells treated with AZT to inhibit protein synthesis were able to elicit a strong specific CTL response in QASQEVKNW specific CTL clone 141 without protein synthesis, while macrophages demonstrated a decreased presentation efficiency.
- Exogenous Gag epitope presentation was Env-dependent and required receptor-dependent fusion.

**HXB2 Location** p24 (176–184)

**Author Location** p24 (308–316)

**Epitope** QATQEVKNW

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B53)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B53 women, 1/2 HEPS and 7/9 HIV-1 infected women recognized this epitope.

**HXB2 Location** p24 (176–184)

**Author Location** p24 (308–316 subtype A consensus)

**Epitope** QATQEVKNM

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Keywords** binding affinity, subtype comparisons

**References** Dorrell *et al.* 2001

- In clade A infected Gambians, three HLA-B53 epitopes were defined in Gag p24 using ELISPOT, tetramer, and cytotoxicity assays.
- Two of the new epitopes lacked the predicted P2 anchors, DTI-NEEAAEW and QATQEVKNM, and bound to B53 with high affinity, thus extending the anchor residue motif for B53 and the related B35.
- While S, T, and P could all fit into the HLA-B35 or HLA-B53 B pocket and form a hydrogen bond, A would not form a bond, so the authors propose compensatory interactions account for the high affinity of QATQEVKNM for B53.
- QATQEVKNM was recognized in 6/7 HLA-B53 subjects.
- Cross-recognition of QATQEVKNM was not studied here, but it was noted that both the A, QATQEVKNM, and B, QASQD-VKNW, subtype version of this epitope, are also presented by HLA-B57 and B58, common HLA alleles in Africans.

**HXB2 Location** p24 (176–184)

**Author Location** p24

**Epitope** QASQEVKNW

**Epitope name** B53-QW9(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (176–184)

**Author Location**

**Epitope** QATQEVKNN

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining

**Keywords** responses in children, rate of progression

**References** Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking attribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Response detected in 2 LTNP children.

**HXB2 Location** p24 (176–184)

**Author Location**

**Epitope** QASQEVKNN

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53, B57, Cw04)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope QASQEVKNN when restricted by HLA-B53, elicited a magnitude of response of 595 SFC with a functional avidity of 0.1nM and binding affinity of 9.7nM. When restricted by HLA-B57, it elicited a magnitude of response of 350 SFC with a functional avidity of 10nM and binding affinity of 157nM. When restricted by HLA-Cw04, it elicited a magnitude of response of 755 SFC with a functional avidity of 0.05nM.

**HXB2 Location** p24 (176–184)

**Author Location**

**Epitope** QASQEVKNN

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53, B57, Cw04)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA associations (B53, B57, Cw04), an additional HLA (B58) was statistically predicted to be associated with this epitope.

**HXB2 Location** p24 (176–184)

**Author Location** Gag (304–321 B con)

**Epitope** QASQEVKNN

**Epitope name** QW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53, B58)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** variant cross-recognition or cross-neutralization

**References** Draenert *et al.* 2004c

- CD8+ T-cell responses that persisted in individuals with advanced disease were studied; most of the optimal epitopes defined were recognized with intermediate to high avidity. On average 13 (range, 2-39) epitopic regions were targeted in an average of 6 proteins (range, 1-8). HAART resulted in decrease in antigen and reduction in gamma IFN EliSpot responses, suggesting active responses to autologous virus. The lack of mutations within most viral epitopes suggest that persistent CTL through late disease do not exert strong immune selection pressure, yet the Elispot assays show robust responses, suggesting to the authors that gamma IFN-based screening methods may not reveal functional CD8+ T-cell impairment in patients with AIDS.
- 2 subjects recognized this epitope with high functional avidity. Autologous sequence revealed no substitutions in this epitope compared to the B consensus.

**HXB2 Location** p24 (176–184)

**Author Location** Gag (SF2)

**Epitope** QASQEVKNN

**Epitope name** QW9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** acute/early infection

**References** Goulder *et al.* 2001a

- This peptide elicited a weak CTL response during acute infection of patient PI004.

- Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond.

**HXB2 Location** p24 (176–184)

**Author Location** p24 (176–184)

**Epitope** QASQEVKNW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 6/7 patients recognized this epitope.

**HXB2 Location** p24 (176–184)

**Author Location** Gag

**Epitope** QASQEVKNW

**Epitope name** QW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 5, qasqDvknw, was found in the most polymorphic residue in the epitope. This was shared between clades B and C. The most common substitution in people carrying B57 was in position 3, qaTqevknw.

**HXB2 Location** p24 (176–184)

**Author Location** p24 (308–316)

**Epitope** QATQDVKNW

**Epitope name** QW9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Ethiopia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization

**References** Currier *et al.* 2005

- Epitope sequence variation and CD8 T-cell responses were analyzed in C subtype infected HLA-B57-positive individuals from Ethiopia. KF11 was the immunodominant response.
- QATQDVKNW had a single variant, D5E (QATQEVKNW) in 1 subject; there was no apparent immune selection in this epitope. The QW9 peptide was tested in 2 B57-positive subjects; neither responded.

**HXB2 Location** p24 (176–184)

**Author Location**

**Epitope** QASQEVKNW

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** p24 (176–184)

**Author Location**

**Epitope** QASQEVKNW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** responses in children, mother-to-infant transmission

**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

**HXB2 Location** p24 (176–184)

**Author Location** (LAI)

**Epitope** QASQEVKNW

**Subtype** B

**Immunogen**

**Species (MHC)** human (Cw4)

**References** Buseyne 1999

**HXB2 Location** p24 (176–184)  
**Author Location** p24 (176–184)  
**Epitope** QASGEVKNW  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (Cw4)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** p24 (176–184)  
**Author Location** p24  
**Epitope** QASQEVKNW  
**Subtype** B, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B53, Cw4)  
**Donor MHC** A23, A24, B35, B58, Cw4, Cw7; A23, A34, B44, B53, Cw4, Cw6  
**Country** Democratic Republic of the Congo  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization  
**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from two infected people carrying subtype D Gag. The epitope sequence in one person matched the peptide, in the other had an E5D change, QASQdVKNW.

**HXB2 Location** p24 (176–184)  
**Author Location** Gag  
**Epitope** QASQEVKNW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** assay standardization/improvement, epitope processing, characterizing CD8+ T cells  
**References** Beattie *et al.* 2004

- This study compared CD8+ T cell EliSpot responses to 58 Gag peptides that were optimal epitopes, with responses to overlapping 15 mers that spanned Gag. When screening for HIV-1-specific CD8 T-cell responses from 49 HIV+ people, overlapping 15-mer peptide pools revealed several novel responses that would have been missed using predefined CD8 epitopes. However, the 15-mer pools often missed low-level responses

to predefined epitopes, especially when the epitope was located centrally in the 15-mer peptide, and the overall level of response to the 15 mers was generally lower (mean 1.4 fivefold dilutions lower, range 0–3).

- In one individual, a response to QASQEVKNW could be detected at a concentration of 0.2  $\mu$ g/ml, while a response to RAEQASQEVKNWMTE required 25  $\mu$ g/ml for detection.

**HXB2 Location** p24 (176–185)  
**Author Location** p24 (311–319 SF2)  
**Epitope** QASKEVKNWV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/2 group 3.

**HXB2 Location** p24 (177–185)  
**Author Location** p24 (177–185)  
**Epitope** ATQEVKNWM  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (B53)  
**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance  
**References** Kaul *et al.* 2001a

- Variants A(T/S)QEVKNWM are specific for the A/B clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B53 women, 1/2 HEPS and 5/9 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in the 1/2 HEPS case and in only one of the 5/9 HIV-1 infected women.

**HXB2 Location** p24 (179–189)  
**Author Location** Gag (312–322 SIV)  
**Epitope** AAVKNWMTQTL  
**Epitope name** AL11  
**Immunogen**  
**Species (MHC)** (H2-Db)  
**Donor MHC** A\*0101, A\*0201, B\*0801, B\*50, Cw\*0602, Cw\*0701  
**References**

**HXB2 Location** p24 (179–189)  
**Author Location** Gag (312–322 SIV)  
**Epitope** AAVKNWMTQTL  
**Epitope name** AL11  
**Immunogen** vaccine  
*Vector/Type:* DNA, DNA prime with virus-like particle (VLP) boost *Strain:* SIV  
*HIV component:* Gag  
**Species (MHC)** mouse (H2-Db)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining  
**Keywords** vaccine-induced epitopes, immunodominance, vaccine antigen design, SIV  
**References** Liu *et al.* 2006a

- An SIV Gag DNA vaccine was studied in mice in order to enhance subdominant immune responses to the KV9 epitope, without compromising its immunodominant response to the Gag AL11 epitope. Both epitopes share a common MHC restricting allele. Novel vaccine strategies including anatomic separation and heterologous prime-boost were investigated to expand vaccine-elicited CTL responses. This was the first study of its kind using DNA gene-based vaccines.
- This immunodominant epitope, AAVKNWMTQTL (AL11), was omitted from the initial vaccination administered, rendering the mouse incapable of recognizing it or the mutated peptide AAVKaWMTQTL, and allowing instead a dramatic, sustained response to the subdominant epitope studied.
- The immunodomination of AL11 over the subdominant epitope (KV9) was found to be a local rather than systemic mechanism, depending on anatomic the site of vaccine administration.

**HXB2 Location** p24 (180–189)  
**Author Location** p24 (313–322)  
**Epitope** EVKNWMTETL  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (B53)  
**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance  
**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** p24 (181–190)  
**Author Location** p24 (313–322 LAI)  
**Epitope** VKNWMTETLL  
**Subtype** B  
**Immunogen**

**Species (MHC)** human (B8)  
**References** Brander & Walker 1996  
 • P. Johnson, pers. comm.

**HXB2 Location** p24 (181–191)  
**Author Location** p24 (181–191)  
**Epitope** VKNWMTETLLV  
**Epitope name** VV11  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*27 motif)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** binding affinity, subtype comparisons, acute/early infection  
**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- Epitope sequences for this epitope, VV11 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen only to the A-clade variant. Anchor residues are at positions 2, 9 and 10; while the C-clade variant contains a semi-conservative change at position 7 to VKNWMTdTLV.

**HXB2 Location** p24 (185–202)  
**Author Location** (C consensus)  
**Epitope** MTDTLVQANPDCKTIL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** p24 (190–199)  
**Author Location** Gag (Henan isolate)  
**Epitope** LVQNSNPDCCK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p24 (191–199)**Author Location** p24 (323–331 Henan isolate)**Epitope** VQNSNPDCCK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A11)**Country** China**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- Newly identified HLA-A11-restricted epitope.
- VQNSNPDCCK was 1 of 2 most frequently recognized peptides restricted by HLA-A11 (54%).

**HXB2 Location** p24 (191–205)**Author Location** p24 (191–205)**Epitope** VQANPDCKTILKAL**Immunogen** HIV-1 infection**Species (MHC)** human (B51)**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (191–205)**Author Location** p24 (323–337)**Epitope** VQANPDCKTILKAL**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**References** Nixon & McMichael 1991

- Two CTL epitopes defined (see also p17(21–35))

**HXB2 Location** p24 (191–205)**Author Location** p24 (325–339 SF2)**Epitope** VQANPDCKTILKAL**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Keywords** review, immunodominance, escape**References** Goulder *et al.* 1997a; Phillips *et al.* 1991

- Longitudinal study of CTL escape mutants in people with the appropriate HLA types – little variation was observed in the immunodominant B27 epitope, relative to the B8 epitopes, which varied over time.
- Goulder *et al.* [1997a] is a review of immune escape that points out that there may be a protective effect associated with B27, and that HLA-B8 individuals tend to progress more rapidly than HLA B27 patients.

**HXB2 Location** p24 (191–205)**Author Location** Gag (320–328 BH10, LAI)**Epitope** VQANPDCKTILKAL**Immunogen** HIV-1 infection**Species (MHC)** human**References** Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is TLLVQ-NANP) has similarity with growth differentiation factor 11, fragment THLVQQANP.

**HXB2 Location** p24 (191–210)**Author Location** p24 (323–342 SF2)**Epitope** VQANPDCKTILKALGPAAT**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- Three of these 12 had CTL response to this peptide.
- The responding subjects were HLA-A3, A24, B8, B55; HLA-A1, A11, B8, B27.

**HXB2 Location** p24 (191–210)**Author Location** p24 (323–342 SF2)**Epitope** VQANPDCKTILKALGPAAT**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** p24 (193–201)**Author Location** Gag (327–335 SF2)**Epitope** NANPDCKTI**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5101)**Keywords** subtype comparisons, rate of progression**References** Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996; Lancet 22:1187, 1986; Hum Immunol 22:73, 1988; Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%



- Of the 172 HIV-1 peptides with HLA-B\*5101 anchor residues, 33 bound to HLA-B\*5101, seven of these peptides were reactive with CTL from 3 B\*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences, NANPDCKTI is conserved.

**HXB2 Location** p24 (193–201)  
**Author Location** p24 (193–201)  
**Epitope** NANPDCKTI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5101)  
**Donor MHC** A\*0201, A\*31, B\*27, B\*5101, Cw\*02; A\*2402, A\*26, B\*07, B\*5101, Cw\*07  
**Country** Japan  
**Assay type** Chromium-release assay  
**Keywords** epitope processing, escape  
**References** Yokomaku *et al.* 2004

- Epitope variants escaped from being killed by CTLs in an endogenous expression system although they were recognized when corresponding synthetic peptides were exogenously loaded onto the cells. Escape is thus probably due to changes that occur during the processing and the presentation of epitopes in infected cells.
- Epitope variant nSnpdckNi was not recognized when added exogenously or when processed endogenously, but the mutations were in anchor residues and presumably inhibited binding to B\*5101.

**HXB2 Location** p24 (193–201)  
**Author Location** p24 (325–333)  
**Epitope** NANPDCKTI?  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Keywords** immunodominance  
**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 3/11 of the HLA A2+ individuals were HLA B51 and two of these responded to this epitope as well as to other epitopes.

**HXB2 Location** p24 (193–201)  
**Author Location** p24 (324–335 IIIB)  
**Epitope** NANPDCKTI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Keywords** responses in children, mother-to-infant transmission, escape  
**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- No variants of this epitope were found in a non-transmitting mother that had a CTL response to this epitope.

**HXB2 Location** p24 (193–201)  
**Author Location** p24 (323–333)  
**Epitope** NANPDCKTI  
**Epitope name** NAN  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Keywords** HAART, ART, acute/early infection  
**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B51+

**HXB2 Location** p24 (193–201)  
**Author Location** p24 (193–201)  
**Epitope** NANPDCKTI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, escape  
**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** p24 (193–201)  
**Author Location** p24 (193–201)  
**Epitope** NANPDSKTI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Donor MHC** A\*3101, A68, B\*4403, B51  
**Keywords** supervised treatment interruptions (STI)  
**References** Arnedo-Valero *et al.* 2004

- T cell immune responses following STI were monitored in two chronically HIV-1 infected partners (A and B) who had contracted HIV-1 in 1992. STI induced strong transitory CD4+ and CD8+ T cell responses in both patients. Patient A displayed broad CD8+ T cell responses directed against Env, Pol, Gag, and Nef HIV-1 antigens. CTL responses in patient B were directed against two epitopes: Gag(p24)NANPDSKTI and Pol(RT)EELRQHLLRW.

- HXB2 Location** p24 (193–201)  
**Author Location** p24  
**Epitope** NANPDCKTI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Donor MHC** A01, A32, B\*1410, B15; A\*3101, A68, B\*4403, B51  
**Country** Spain  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** HAART, ART, supervised treatment interruptions (STI)  
**References** Arnedo-Valero *et al.* 2004
- T cell immune responses following STI were monitored in two chronically HIV-1 infected partners (A and B) who had contracted HIV-1 during 1992. STI induced strong transitory CD4+ and CD8+ T cell responses in both patients. The viruses remained very closely related over 10 years, despite the two individuals having different HLA types; the authors suggest the maintained similarity does not support a strong role for HLA driven HIV diversity as has been claimed in Moore *et al.* (Science 2002).
  - During the second treatment stop, patient A developed a strong proliferative response to p24, and multiple strong CD8+ T cell responses to Env, Pol, Gag and Nef. This patient was able to control viral load for two years follow up without therapy. Patient B developed a very weak CD4+ T cell response against p24 during breaks in therapy, and had CD8+ responses to two epitopes. Patient A: A01, A32, B\*1410, B15; Patient B: A\*3101, A68, B\*4403, B51.

- HXB2 Location** p24 (193–201)  
**Author Location** p24 (191–205)  
**Epitope** NANPDCKTI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Ferrari *et al.* 2000
- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

- HXB2 Location** p24 (194–202)  
**Author Location** p24 (194–202)  
**Epitope** ANPDCKTIL  
**Epitope name** ANP  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, escape  
**References** Oxenius *et al.* 2004b
- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0–80% as efficiently as the index peptide, and the relative efficiency of the variant epitopes increased using

PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.

- This was one of 8 reactive epitopes found not to vary over time.

- HXB2 Location** p24 (195–202)  
**Author Location** (C consensus)  
**Epitope** NPDCKTIL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - Mutational patterns in the T6 residue of NPDCKTIL are associated with the presence of the HLA presenting molecule in the host.

- HXB2 Location** p24 (195–202)  
**Author Location** p24 (323–342)  
**Epitope** NPDCKTIL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**References** Bernard *et al.* 1998
- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population.
  - No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs.
  - Epitope sequences were deduced from larger reactive peptides based on HLA binding motifs – XPXXXXXL is a B35 binding motif.

- HXB2 Location** p24 (195–202)  
**Author Location**  
**Epitope** NPDCKTIL  
**Epitope name** Gag-NL8  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**References** Sabbaj *et al.* 2003
- Among HIV+ individuals who carried HLA B35, 3/17 (18%) recognized this epitope.

- HXB2 Location** p24 (195–205)  
**Author Location** (C consensus)  
**Epitope** NPDCKTILRAL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3910)

- Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - NPDKTILRAL is an optimal epitope.
- HXB2 Location** p24 (196–204)  
**Author Location** Gag (328–336)  
**Epitope** PDCKTILKA  
**Subtype** B
- Immunogen** HIV-1 infection, peptide-HLA interaction  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** immunodominance  
**References** Rolland *et al.* 2007b
- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
  - Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
  - This HIV-1 epitope, PDCKTILKA, is similar to human protein Deltex 4 homolog, sequence HPDCKTI.
- HXB2 Location** p24 (197–205)  
**Author Location** p24 (329–337 LAI)  
**Epitope** DCKTILKAL  
**Subtype** B
- Immunogen**  
**Species (MHC)** human (B\*0801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is a B\*0801 epitope.
- HXB2 Location** p24 (197–205)  
**Author Location** p24 (329–337 LAI)  
**Epitope** DCKTILKAL  
**Subtype** B
- Immunogen**  
**Species (MHC)** human (B8)  
**References** Sutton *et al.* 1993
- Predicted epitope based on B8-binding motifs, from larger peptide VQNANPDCKTILKAL.
- HXB2 Location** p24 (197–205)  
**Author Location** p24 (329–337)  
**Epitope** DCKTILKAL
- Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** escape  
**References** Nowak *et al.* 1995
- In a longitudinal study of CTL response and immune escape – the variant DCRTILKAL was also found, binds to B8, but is not recognized.
- HXB2 Location** p24 (197–205)  
**Author Location** p24 (329–337)  
**Epitope** DCKTILKAL
- Immunogen**  
**Species (MHC)** human (B8)  
**References** McAdam *et al.* 1995
- Defined as minimal epitope by titration and binding studies.
- HXB2 Location** p24 (197–205)  
**Author Location** p24 (197–205)  
**Epitope** DCKTILKAL
- Immunogen**  
**Species (MHC)** human (B8)  
**References** Goulder *et al.* 1997g
- Included in a study of the B8 binding motif.
- HXB2 Location** p24 (197–205)  
**Author Location** p24 (329–337)  
**Epitope** DCKTILKAL
- Epitope name** DCK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection  
**References** Oxenius *et al.* 2000
- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
  - This epitope was recognized at a low level by only 1 of the 7/8 study subjects that were HLA B8.
  - Patient SC12(HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKKKYKLLK – GEIYKRWII and GGKKKYKLLK responses were stimulated by a brief period off therapy.
- HXB2 Location** p24 (197–205)  
**Author Location** p24 (197–205)  
**Epitope** DCKTILKAL
- Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (197–205)

**Author Location** p24 (197–205)

**Epitope** DCKTILKAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

**HXB2 Location** p24 (197–205)

**Author Location** p24

**Epitope** DCKTILKAL

**Epitope name** DCK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** p24 (197–205)

**Author Location** Gag (329–337)

**Epitope** DCKTILKAL

**Immunogen** HIV-1 infection

**Species (MHC)** humanized rabbit (B8)

**Donor MHC** A03, A28, B07, B08

**Country** Canada

**Assay type** proliferation, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, memory cells, immune dysfunction

**References** Gamberg *et al.* 2004a

- HAART restores HIV specific immunity after advanced infection by increase of CD4+ and CD8+ T cell numbers after suppression of viral replication. However, HIV specific CTLs emerged only with detectable viral replication breakthroughs and were short-lived while CD4+ T-cell responses remained compromised, suggesting failure of generating stable CD8+ memory T-cells in the absence of HIV-specific T-helper responses.

**HXB2 Location** p24 (197–205)

**Author Location** (B consensus)

**Epitope** DCKTILKAL

**Epitope name** DL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A01, A03, B08, B14, Cw7, Cw8

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN- $\gamma$  and TNF- $\alpha$  exhibit stronger cytotoxic activity than those secreting only IFN- $\gamma$ . These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** p24 (197–205)

**Author Location** p24

**Epitope** DCKTILKAL

**Epitope name** B8-DL9(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (197–205)

**Author Location**

**Epitope** DCKTILKAL

**Immunogen**

**Species (MHC)** (B8)

**Keywords** review, immunodominance, escape, vaccine antigen design

**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

**HXB2 Location** p24 (197–211)

**Author Location** Gag (329–343)

**Epitope** DCKTILKALGPAATL

**Epitope name** DL15

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape  
**References** Bailey *et al.* 2006b
- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
  - One subject responded to peptide DL15, a non-B\*57-restricted peptide.
- HXB2 Location** p24 (199–218)  
**Author Location** Gag (331–350)  
**Epitope** KTLRALGPGATLEEMMTAC  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons  
**References** Novitsky *et al.* 2002
- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
  - Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
  - This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.
- HXB2 Location** p24 (203–211)  
**Author Location** Gag (335–343 SUMA)  
**Epitope** KALGPAATL  
**Epitope name** Gag KL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells  
**References** Jones *et al.* 2004
- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- HXB2 Location** p24 (204–214)  
**Author Location** Gag (343–353)  
**Epitope** ALGPGASLEEM  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005
- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
  - 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.
- HXB2 Location** p24 (206–214)  
**Author Location** Gag (338–346)  
**Epitope** GPGATLEEM  
**Subtype** A, C, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702, B\*5801, B\*8101)  
**Country** Tanzania  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** rate of progression, immunodominance  
**References** Geldmacher *et al.* 2007b
- The objectives of this study were to find antiviral epitopic determinants of Gag HIV-specific CTL response and to find 'host HLA-CTL response' correlations. By studying 56 ART-naive subjects including low viral load (LVL) responders, the authors show that subjects expressing the above "protective" HLA have broader Gag epitope recognition which may be abrogated if co-expressed with HLA-B alleles associated with rapid AIDS progression. Also, a negative linear relation was seen between Gag epitope numbers recognized and plasma viral load while a positive relationship was seen with CD4 T-cell count. Finally, LVL subjects recognized specific Gag regions at the N- and C-termini of the protein more often than peptides in the middle of the protein.
  - Epitope GPGATLEEM, supposedly presented by HLA-B\*8101 is strongly associated with LVL. However, the second position GpGATLEEM is highly variable.
- HXB2 Location** p24 (208–226)  
**Author Location** Gag

**Epitope** AATLEEMMTACQGVGGPSH

**Epitope name** GAG-47

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpr, Vpu and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, aAtLEEMMTACQGVGGPSH differs from the consensus C sequence gAsLEEMMTACQGVGGPSH at 2 amino acid positions, i.e. by 10.5%.

**HXB2 Location** p24 (209–217)

**Author Location** Gag

**Epitope** ATLEEMMTA

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0206)

**Country** Thailand

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** optimal epitope

**References** Kantakamalakul *et al.* 2006

- T cell responses in CRF01\_AE infected individuals from Thailand were studied. Fine mapping of the peptides containing potentially novel epitopes revealed novel restriction of a previously identified epitope in this population.
- A novel restriction allele for this epitope (ATLEEMMTA) was found, HLA-A\*0206.

**HXB2 Location** p24 (209–217)

**Author Location** Gag (341–)

**Epitope** ATLEEMMTA

**Epitope name** Gag341

**Immunogen** HIV-1 infection, vaccine

**Vector/Type:** peptide **HIV component:** p24

**Gag Adjuvant:** Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder that did not induce CTL and CD8+ T-cell IFN gamma responses in mice, although responses were detected in 2/17 HIV+ HLA-A2 subjects.

**HXB2 Location** p24 (211–230)

**Author Location** p24 (343–362 SF2)

**Epitope** LEEMMTACQGVGGPGHKARV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** McAdam *et al.* 1998

**HXB2 Location** p24 (211–230)

**Author Location** p24 (345–364 SF2)

**Epitope** LEEMMTACQGVGGPGHKARV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** van Baalen *et al.* 1993

- Gag CTL epitope precursor frequencies estimated, peptide mapping.

**HXB2 Location** p24 (211–231)

**Author Location** p24 (343–362 SF2)

**Epitope** LEEMMTACQGVGGPGHKARVL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI gag.
- One of these 12 had CTL response to this peptide.
- The responding subject was HLA-A1, A2, B50, B57.

**HXB2 Location** p24 (212–222)

**Author Location** Gag (347–357)

**Epitope** EEMMTACQGVG

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p24 (213–221)

**Author Location** Gag

**Epitope** EMMTACQGV

**Epitope name** E9V

**Immunogen** vaccine

*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140 $\Delta$ V3

**Species (MHC)** transgenic mouse (A\*0201)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells

**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** p24 (213–221)

**Author Location** Gag (345–)

**Epitope** EMMTACQGV

**Epitope name** Gag345

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* p24 Gag *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced a response in 1/6 transgenic mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.

**HXB2 Location** p24 (217–227)

**Author Location** p24 (217–227)

**Epitope** ACQGVGGPGHK

**Epitope name** AK11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*11)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, subtype comparisons, acute/early infection

**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.

- Epitope sequences for this epitope, AK11 are invariant between CON B, COT B, ANC B and M-group. Cross-recognition is seen only to the A-clade variant. An anchor residue is at position 11; while the C-clade variant contains a semi-conservative change at position 9 to ACQGVGGPShk.

**HXB2 Location** p24 (217–227)

**Author Location** p24 (349–359 IIIB)

**Epitope** ACQGVGGPGHK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*1101 epitope.

**HXB2 Location** p24 (217–227)

**Author Location** Gag (349–359)

**Epitope** ACQGVGGPGHK

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** subtype comparisons, TCR usage

**References** Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A\*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A\*1101 epitopes was recognized in a clade specific manner. Two other HLA A\*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- ACQGVGGPGHK was found to elicit clade-specific responses in clade B (ACQGVGGPGHK is most common in clades A and B) and clade E (acqvggpgshk is most common and is also common in clades C and D). ACQGVGGPGHK was recognized by CTL from 4/5 B clade infected Japanese

subjects, and acqgvggpShk from 3/7 E clade infected Thai subjects.

- The binding of the two variants to HLA A\*1101 was almost identical, but bulk CTL generated from individuals did not cross-react with the cross-clade peptides, indicating the lack of cross-reactivity was due to TCR specificity.

**HXB2 Location** p24 (217–227)

**Author Location** Gag (349–359 SUMA)

**Epitope** ACQGVGGPGHK

**Epitope name** Gag AK11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1103)

**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** p24 (217–227)

**Author Location** p24 (349–359 IIIIB)

**Epitope** ACQGVGGPGHK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Sipsas *et al.* 1997

- HIV IIIIB proteins were used to define the range of CTL epitopes recognized by three lab workers accidentally infected with HIV-1 IIIIB.
- ACQGVGGPSHK, a variant found in HIV RF, was also recognized.

**HXB2 Location** p24 (217–227)

**Author Location** p24 (SF2)

**Epitope** ACQGVGGPGHK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** subtype comparisons, immunodominance

**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71–85), SALSEGATPQDLNMLNTVG (p24 41–60), and WEKIRL-RPGGKKKYKLLK (p17 16–30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20–36), ELRSLYNTVATLYCV (p17Gag 74–88), SALSEGATPQDLNMLNTVG (p24 41–60), FRDYVDRFFKTLRAEQA (p24 161–177), and SILDIKQGKEPFRDY (p24 149–164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (217–227)

**Author Location** p24 (349–359)

**Epitope** ACQGVGGPGHK

**Epitope name** ACQ

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** SC19: A\*11, A\*29, B\*08, B\*44, Cw\*06, Cw\*0701, DQ2, DQ8, DR3, DR52, DR53, DR7; SC18: A\*02, A\*11, B\*50, B\*58, Bw4, Bw6, Cw\*0401, Cw10, DQ2, DQ8, DR3, DR4, DR52, DR53

**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- Both of the 2/8 HLA-A11 study subjects recognized this CTL epitope.
- Patient SC19 (HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGGEFFY that declined during therapy initiated at day 197.
- Patient SC18 (HLA A2/11, B8/44, Cw06/0701, DR3/7, DR52/53, DQ2) recognizes the epitopes ACQGVGGPGHK, QVPLRPMTYK, AVDLSHFLK, and one called QIY but not fully described – he had brief therapy upon seroconversion and has had low viral load during 600 days of follow up.

**HXB2 Location** p24 (217–227)

**Author Location** p24 (216–226)

**Epitope** ACQGVGGPGHK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Ferrari *et al.* 2000



- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** p24 (217–227)

**Author Location** p24 (349–359 SF2)

**Epitope** ACQGVGGPGHK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HAART, ART, acute/early infection

**References** Altfield *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who seroconverted to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 2/2 group 3.

**HXB2 Location** p24 (217–227)

**Author Location** p24

**Epitope** ACQGVGGPGHK

**Epitope name** ACQ

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** p24 (217–227)

**Author Location** (B consensus)

**Epitope** ACQGVGGPGHK

**Epitope name** AK11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A29, B08, B44, Cw4, Cw7

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN- $\gamma$  and TNF- $\alpha$  exhibit stronger cytotoxic activity than those secreting only IFN- $\gamma$ . These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** p24 (217–227)

**Author Location** Gag (349–359)

**Epitope** ACQGVGGPGHK

**Epitope name** AK11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** escape, TCR usage, variant cross-recognition or cross-neutralization, optimal epitope

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent maturation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wild type, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wild type.
- A novel CD8 T-cell response was generated against the escape variant acqgvggpShk.
- Additional analyses showed that the majority of individuals expressing HLA-A11 targeted the acqgvggpShk variant sequence while the wild-type sequence was less frequently recognized.

**HXB2 Location** p24 (217–227)

**Author Location** Gag

**Epitope** ACQGVGGPGHK

**Epitope name** AK11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.

- One escape mutation, at position 9, acqgvvgpShk, was found in the most polymorphic residues in the epitope. These were shared between clades B and C.

**HXB2 Location** p24 (217–227)

**Author Location** p24

**Epitope** ACQGVGGPGHK

**Epitope name** A11-AK11(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (218–227)

**Author Location** Gag (350–359 Henan isolate)

**Epitope** CQGVGGPGHK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- CQGVGGPGHK was 1 of 2 most frequently recognized peptides restricted by HLA-A11 (59%).

**HXB2 Location** p24 (220–227)

**Author Location** p24

**Epitope** GVGPGGPHK

**Epitope name** A11-GK8(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (220–229)

**Author Location** Gag (Henan isolate)

**Epitope** GVGPGGPHKAR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p24 (221–231)

**Author Location** p24 (353–363 LAI)

**Epitope** VGGPGGPHKARVL

**Epitope name** G1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** HAART, ART

**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** p24 (223–231)

**Author Location** (LAI)**Epitope** GPGHKARVL**Subtype** B**Immunogen****Species (MHC)** human (B\*0702)**Keywords** optimal epitope**References** Frahm *et al.* 2008; Goulder 1999

- C. Brander notes this is a B\*0702 epitope.

**HXB2 Location** p24 (223–231)**Author Location** p24 (223–231 SF2)**Epitope** GPGHKARVL**Epitope name** GL9**Immunogen** HIV-1 infection**Species (MHC)** human (B\*0702)**References** Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- The response to GPGHKARVL was dominant.

**HXB2 Location** p24 (223–231)**Author Location** (C consensus)**Epitope** GPSHKARVL**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*0702)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** characterizing CD8+ T cells**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p24 (223–231)**Author Location** (C consensus)**Epitope** GPGHKARVL**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*0702)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the G3 residue of GPGHKARVL are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** p24 (223–231)**Author Location** (C consensus)**Epitope** GPSHKARVL**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*0702)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- GPSHKARVL is an optimal epitope.

**HXB2 Location** p24 (223–231)**Author Location** (224–232)**Epitope** GPSHKARVL**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*0702)**Assay type** Other**Keywords** HLA associated polymorphism**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- GPSHKARVL was a previously defined B\*0702 presented epitope that encompassed a B\*07- associated polymorphism, GPsHKARVL, in the third position.

**HXB2 Location** p24 (223–231)**Author Location** p24 (1858–)**Epitope** GPGHKARVL**Immunogen** HIV-1 infection**Species (MHC)** human (B\*0702)**Country** Australia**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape, HLA associated polymorphism**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., *Science* 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The third position of this epitope GPgHKARVL has a mutational pattern that is correlated HLA B\*0702. This epitope was experimentally tested using IFN-gamma Elispot and functional avidity studies.

**HXB2 Location** p24 (223–231)

**Author Location** Gag (355–363)

**Epitope** GPGHKARVL

**Epitope name** GL9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702, B\*4201)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other

**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism

**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- A strong negative association between B\*0702 and conservation of sequence is observed.

**HXB2 Location** p24 (223–231)

**Author Location** Gag (355–363)

**Epitope** GPSHKARVL

**Subtype** A, C, D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07, B\*42, B\*81)

**Country** Tanzania

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, immunodominance

**References** Geldmacher *et al.* 2007a

- To assess whether T-cell specific responses to Gag and Nef are biased towards infecting subtype recombination, 56 ART-naive subjects were studied using six overlapping peptide sets consisting 15-mer peptides, covering both proteins completely. A multi-region hybridization assay was employed. Overall,

the best recognized epitope variant in terms of magnitude and breadth corresponded to infecting subtype, in this case usually type-C. Hot spots of CTL recognition in Gag were in p24, p17 and p15; hotspots against Nef were in its central, conserved region.

- Epitope variants GPgHKARVL and GPgHKARVL were studied as peptide sequences ACQGVG-GPgHKARVL (subtypes C and D) and ACQGVG-GPgHKARVL (subtype A) with 12.5% responders. Subtypes C and D were best recognized.

**HXB2 Location** p24 (223–231)

**Author Location**

**Epitope** GPGHKARVL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B07)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B07), an additional HLA (B40) was statistically predicted to be associated with this epitope.

**HXB2 Location** p24 (223–231)

**Author Location** p17

**Epitope** GPGHKARVL

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p24 (223–231)

**Author Location** p24 (355–363 LAI)

**Epitope** GPGHKARVL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** review, escape  
**References** Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical sibling hemophiliac brothers were both infected with the same batch of factor VIII.
- One had a strong response to this peptide, the other a weak response. They were tested 6-8 years after infection.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

**HXB2 Location** p24 (223–231)  
**Author Location** p24 (SF2)  
**Epitope** GPSHKARVL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** subtype comparisons, immunodominance  
**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study.
- Three peptides GSEELRSYNTVATL (p17 residues 71-85), SALSEGATPQDLNLTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYKLLK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNLTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

**HXB2 Location** p24 (223–231)  
**Author Location** p24 (SF2)  
**Epitope** GPSHKARVL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** subtype comparisons, immunodominance  
**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ Caucasian living in Boston – this epitope did not fall within the three most recognized peptides in the study.
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**HXB2 Location** p24 (223–231)  
**Author Location** p24 (223–231 SF2)  
**Epitope** GPGHKARVL

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 1/4 group 1, 2/3 group 2, and 0/1 group 3.

**HXB2 Location** p24 (223–231)  
**Author Location** p24 (223–231)  
**Epitope** GPGHKARVL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** rate of progression, acute/early infection  
**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconverter homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

**HXB2 Location** p24 (223–231)  
**Author Location** p24 (223–231)  
**Epitope** GPGHKARVL  
**Epitope name** B7-GL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Donor MHC** A3, B7, Cw7  
**Keywords** dynamics, supervised treatment interruptions (STI), immunodominance, acute/early infection  
**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- Only two epitopes were detected during acute infection in patient AC-06, B7 restricted gp41 epitope IPRRIRQGL and Gag GPGHKARVL. GPGHKARVL was the first targeted peptide, and remained immunodominant through the 34 month study period.
- 3/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 1/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** p24 (223–231)

**Author Location** p24 (223–231)

**Epitope** GPGHKARVL

**Epitope name** B7-GL9 Gag

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- In the earliest sample at day18 the sequence for this epitope was gpShkarvl. gpgkharvl dominated at day 606; both were equally well recognized.
- This was an immunodominant epitope, and was present in both viruses, the original strain and the superinfecting strain.

**HXB2 Location** p24 (223–231)

**Author Location** p24 (223–231)

**Epitope** GPGHKARVL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 4/7 patients recognized this epitope.

**HXB2 Location** p24 (223–231)

**Author Location** (B consensus)

**Epitope** GPGHKARVL

**Epitope name** GL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A03, B07, Cw7

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** p24 (223–231)

**Author Location** Gag (355–363)

**Epitope** GPGHKARVL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** p24 (223–231)

**Author Location** p24

**Epitope** GPGHKARVL

**Epitope name** B7-GL9(p24)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p24 (223–231)

**Author Location** Gag

**Epitope** GPGHKARVL

**Epitope name** B7-GL9 Gag (353-363)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44, B7)

**Donor MHC** A02, A32, B27, B39; A03, B07, B51

**Country** France

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, immunodominance, characterizing CD8+ T cells

**References** Almeida *et al.* 2007

- Since it is suggested that a single response to B27-KK10 epitope may be responsible for the association of HLA-B\*2705 patients with AIDS-free survival, B27-KK10-specific CTLs were compared to other HLA-specific CTLs in phenotype, function, clonal diversity, and antigen sensitivity in 47 treatment-naïve infected slow or nonprogressing patients.
- cVL, the cell-associated viral load (number of infected cells harboring HIV DNA) correlated inversely with Gag-specific CTLs. This was most significant in HLA-B27 donors, and KK10 was identified as the peptide generating strongest CTL responses.
- B27-KK10-specific CTLs had no significant phenotypic differences from other epitope-specific CTLs upon testing a large panel of markers; however, they released higher proportions of IFN- $\gamma$ , TNF- $\alpha$ , MIP-1 $\beta$  and CD107a upon antigenic stimulation.
- Both B27-KK10-specific and other HLA-specific CTLs had strikingly consistent domination of single clonotypes, as shown by analyses of TCRB gene expression. B27-KK10-specific CTLs showed no preferential usage of CDR3 motifs, indicating that they could be recognized by diverse clonotypes with differing binding properties. Over several years, B27-KK10-specific CTLs changed their dominant clonotype as compared to other CTLs. This temporal dominant clonal turnover was attributed to a decline in replicative capacity of the dominant clonotype as seen by increases in CD57 expression, which is linked to replicative senescence.
- Studies involving functional avidity and different HLA-restricted responses proved that B27-KK10 responses had highest avidity. An inverse correlation between patient cVL and functional avidity of both dominant and highest subdominant responses suggested that functional avidity correlates with capacity to control HIV replication via infected cell elimination.
- Using the example seen in one patient, the authors stress the importance of maintaining protective stimulating activity of

CTLs. When control by dominant clonotypes is lost, as in viral escape, ensuing viral replication is rapid.

- GPGHKARVL, was a dominant epitope found in non-B27-KK10 CTL responses.

## II-B-4 Gag p24-p2p7p1p6 CTL/CD8+ epitopes

**HXB2 Location** p24-p2p7p1p6 (223–1)

**Author Location** Gag

**Epitope** GPGHKARVLA

**Immunogen**

**Species (MHC)** human (B7)

**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFN $\gamma$  production in an ELISPOT assay.
- GPGHKARVLA was confirmed as an HLA-B7 epitope in this study, and had been previously published.

**HXB2 Location** p24-p2p7p1p6 (223–1)

**Author Location** Gag

**Epitope** GPGHKARVLA

**Epitope name** 1291

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A03, A24, B07, B38, Cw07, Cw12/13; A01, A03, B07, B08, Cw03, Cw07

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for GPGHKARVLA: 28%

**HXB2 Location** p24-p2p7p1p6 (225–8)

**Author Location** Gag (357–372 LAI)

**Epitope** GHKARVLAEATLSQVN

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.

- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM28 (CDC P2A) had a CTL response to four epitopes in Gag.

**HXB2 Location** p24-p2p7p1p6 (229–7)

**Author Location** Gag (361–370)

**Epitope** RVLAEAMSQV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- RVLAEAMSQV was seen in 69% HLA-A2-positive individuals.

**HXB2 Location** p24-p2p7p1p6 (230–7)

**Author Location** Gag (363–370)

**Epitope** VLAEAMSQV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

**HXB2 Location** p24-p2p7p1p6 (230–7)

**Author Location** Gag (386–)

**Epitope** VLAEAMSQV

**Epitope name** Gag-386

**Immunogen**

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity, subtype comparisons, super-type, computational epitope prediction, immunodominance

**References** Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- VLAEAMSQV binds to all five HLA-A2 supertype alleles tested: A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802 (highest affinity)
- 4/22 individuals with chronic HIV-1 infection recognized this epitope, and it was immunodominant in 3/4 by ELISPOT.
- 0/12 acutely infected individuals recognized this epitope.

**HXB2 Location** p24-p2p7p1p6 (230–7)

**Author Location** Gag

**Epitope** VLAEAMSQV

**Epitope name** Gag 386

**Subtype** M

**Immunogen** vaccine, in vitro stimulation or selection, computer prediction

*Vector/Type:* DNA, peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, mouse, humanized mouse (A\*0201)

**Assay type** Cytokine production, T-cell Elispot

**Keywords** subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization

**References** McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A\*0201 and A\*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- A total of 20 variant forms of Gag 386 were identified. More than 95% of the variant epitopes were recognized by CTLs from mice immunized with the parental form.
- Gag 386 epitope (parent or variant form) was present in 97% of HIV sequences of many M group subtypes.

**HXB2 Location** p24-p2p7p1p6 (230–7)

**Author Location**

**Epitope** VLAEAMSQV

**Epitope name** Gag-VV9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 3/29 (10%) recognized this epitope.



- HXB2 Location** p24-p2p7p1p6 (230–7)  
**Author Location** Gag (362–)  
**Epitope** VLAEAMSQV  
**Epitope name** Gag362(9L)  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)
- Species (MHC)** human, transgenic mouse (A2)  
**Assay type** T-cell Elispot, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction  
**References** Corbet *et al.* 2003
- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
  - This peptide was a good A2 binder that induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.
  - The variant vlaeamsqA was also immunogenic in A2 transgenic mice, eliciting a CD8+ T-cell response, as was recognized in 3/17 HIV+ people, including the person that recognized the vlaeamsqV variant.

- HXB2 Location** p24-p2p7p1p6 (230–7)  
**Author Location** p24 (230–238)  
**Epitope** VLAEAMSQV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding  
**Keywords** acute/early infection, optimal epitope  
**References** Altfeld *et al.* 2005
- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection.

- HXB2 Location** p24-p2p7p1p6 (230–7)  
**Author Location** p24-p2p7p1p6 (362–370)  
**Epitope** VLAEAMSQV  
**Epitope name** VV9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A\*02, A\*32, B\*07, B\*40, Cw\*03, Cw\*07  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion  
**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- The mother was A02+ and carried a variant form of the epitope, VLAEAMShV, which she passed to her A02- child. This form persisted in her child for 15 months.

- HXB2 Location** p24-p2p7p1p6 (230–7)  
**Author Location** p24  
**Epitope** VLAEAMSQV  
**Epitope name** A2-VV9(gp24)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
  - The most frequently recognised epitopes also elicited the greatest CTL response.
  - HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
  - HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
  - In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

- HXB2 Location** p24-p2p7p1p6 (230–7)  
**Author Location** p2p7p1p6 (362–370 Henan isolate)  
**Epitope** VLAEAMSQV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006
- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

- While VLAEAMSQV was described previously to have strong CTL response in HLA-A2 individuals, in this study 8 of 13 (61%) A2-positive individuals demonstrated moderate response to this peptide.

**HXB2 Location** p24-p2p7p1p6 (230–7)

**Author Location** Gag (397–405)

**Epitope** VLAEAMSQV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802)

**HXB2 Location** p24-p2p7p1p6 (230–8)

**Author Location** p2p7p1p6 (362–371 Henan isolate)

**Epitope** VLAEAMSQVT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- VLAEAMSQVT was among 5 most recognized peptides (69%).

## II-B-5 Gag p2p7p1p6 CTL/CD8+ epitopes

**HXB2 Location** p2p7p1p6 (1–10)

**Author Location** p2p7p1p6 (1903–)

**Epitope** AEAMSQVTNS

**Epitope name** A\*3101 KR9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4002)

**Country** Australia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, HLA associated polymorphism

**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore *et al.*, Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- Mutational patterns in the ninth position, AEAMSQVTnS, in this epitope are correlated with the host carrying HLA B\*4002.

**HXB2 Location** p2p7p1p6 (1–10)

**Author Location** p2p7p1p6 (1–10)

**Epitope** AEAMSQVTNS

**Immunogen**

**Species (MHC)** human (B\*4501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** p2p7p1p6 (5–13)

**Author Location** p15 (5–13)

**Epitope** SQVTNSATI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, SQVTNSATI, was detected within overlapping peptide EAMSQVTNSATIMMQR.

**HXB2 Location** p2p7p1p6 (5–13)

**Author Location** Gag (SF2)

**Epitope** SQVTNPANI

**Immunogen** vaccine

*Strain:* B clade SF2 *HIV component:* Gag

**Species (MHC)** mouse (H-2D<sup>b</sup>)

**References** Paliard *et al.* 1998

- HIV-1 (SF2)p55gag vaccination of H-2 mice activates a CTL response against this epitope.

- CTL that recognized SQVTNPANI in the context of H-2D<sup>b</sup> cross-reacted with H-2 alloantigens H-2L<sup>d</sup> and an unidentified self-peptide.
- A postulate: heterozygosity at the MHC level could prevent the maturation of some T cell receptor combinations for foreign peptide and self-MHC constructs because of thymic depletion and tolerance.

**HXB2 Location** p2p7p1p6 (8–17)

**Author Location** Gag

**Epitope** TNSANIMMQR

**Epitope name** TR10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A28, A29, B14, B44, Cw8

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 5, tnsaSimmqr, was found in the most polymorphic residues in the epitope. One escape mutation, at position 2, tTsanimmqr, was found not to correspond to the most polymorphic residues in the epitope. This is a novel partially mapped epitope.

**HXB2 Location** p2p7p1p6 (14–28)

**Author Location**

**Epitope** MMQRGNFRNQRKIVK

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120 boost  
*Strain:* Other  
*HIV component:* gp160

**Species (MHC)** human

**Donor MHC** A3, A33; B15 (63), B27

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85–86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** p2p7p1p6 (18–37)

**Author Location** Gag (96ZM651.8)

**Epitope** SNFKGNKRMVKCFNCGKEGH

**Immunogen**

**Species (MHC)** human (A\*020101)

**References** Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 4 of 8 individuals (50%) who were positive for HLA-A\*02011 responded to the peptide SNFKGNKRMVKCFNCGKEGH.

**HXB2 Location** p2p7p1p6 (21–29)

**Author Location** Gag (C-96BW04.09)

**Epitope** KGPRRIVKC

**Epitope name** B1

**Subtype** C

**Immunogen** vaccine

*Vector/Type:* DNA, alphavirus replicon  
*Strain:* C clade C-96BW04.09, C clade C-96BW15C05  
*HIV component:* Gag, Gag-Pol, Pol

**Species (MHC)** mouse (H-2d)

**Assay type** Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, vaccine antigen design

**References** Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- This is a novel epitope.

**HXB2 Location** p2p7p1p6 (21–29)

**Author Location** Gag (C-96BW15C05)

**Epitope** KGPRIIKC

**Epitope name** B2

**Subtype** C

**Immunogen** vaccine

*Vector/Type:* DNA, alphavirus replicon  
*Strain:* C clade C-96BW04.09, C clade C-96BW15C05  
*HIV component:* Gag, Gag-Pol, Pol

**Species (MHC)** mouse (H-2d)

**Assay type** Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, vaccine antigen design

**References** Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- This is a novel immunodominant epitope.

**HXB2 Location** p2p7p1p6 (23–33)

**Author Location** Gag (386–396)

**Epitope** SKRIVKCFNCG

**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 2/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p2p7p1p6 (25–34)  
**Author Location** Gag (Henan isolate)  
**Epitope** KTVKCFNCGR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p2p7p1p6 (38–47)  
**Author Location** p7 (1996–)  
**Epitope** LARNCRAPRK  
**Epitope name** A\*3101 LR9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3101)  
**Country** Australia  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape, HLA associated polymorphism  
**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore *et al.*, *Science* 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.

- The third position of the epitope LARNCRAPRK an HLA-A\*3101 correlated amino acid, however which one of the two common forms, LARNCRAPRK or LAKNCRAPRK, was the escape or and which was the susceptible form depended on the patient tested. Testing was performed by IFN-gamma ELispot (magnitude) and functional avidity studies.

**HXB2 Location** p2p7p1p6 (38–47)  
**Author Location** Gag  
**Epitope** LARNCRAPRK  
**Epitope name** 1331  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A03, A23, B49, B57; A03, A24, B27, B57, Cw13, Cw18; A03, A26, B08, B52  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, computational epitope prediction  
**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for LARNCRAPRK: 35%. Immunodominant epitope.

**HXB2 Location** p2p7p1p6 (38–48)  
**Author Location** Gag (402–412)  
**Epitope** IAKNCRAPRKK  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p2p7p1p6 (42–50)  
**Author Location** p15 (42–50 SF2)  
**Epitope** CRAPRKKGC  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Donor MHC** B14  
**Keywords** immunodominance  
**References** Yu *et al.* 2002b

- 26/57 HIV-1 infected subjects displayed Gag p15-specific CD8+ T-cell IFN $\gamma$  responses were measured by Elispot and intracellular staining. The immunodominant regions targeted by CD8+ T-cells were mapped to three functional domains: the zinc finger structures, the protease cleavage site p7/p1, and to the Vpr binding site in p6.
- p15 contributed on average 17% of the total Gag response (range 0-100%).
- 3 optimal CTL epitopes were mapped within p15: KELY-PLTSL, CRAPRKKGC, and FLGKIWPSYK.
- 2/6 HLA-B14+ subjects recognized this epitope. The binding motif for B14 is C-term Cys, positions 2 and 5 Arg.

**HXB2 Location** p2p7p1p6 (42–50)  
**Author Location** p15 (42–50)  
**Epitope** CRAPRKKGC  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** p2p7p1p6 (42–50)  
**Author Location** (B consensus)  
**Epitope** CRAPRKKGC  
**Epitope name** CC9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Donor MHC** A28, A29, B14, B44, Cw8  
**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells  
**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN- $\gamma$  and TNF- $\alpha$  exhibit stronger cytotoxic activity than those secreting only IFN- $\gamma$ . These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope

**HXB2 Location** p2p7p1p6 (42–50)  
**Author Location** Gag (405–413)  
**Epitope** CRAPRKKGC  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Donor MHC** A28, A29, B14, B44, Cw8  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a

- previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** p2p7p1p6 (43–52)  
**Author Location** Gag (Henan isolate)  
**Epitope** KAPRKKGCWK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p2p7p1p6 (52–61)  
**Author Location** (Henan isolate)  
**Epitope** KCGKEGHQMK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p2p7p1p6 (55–70)  
**Author Location** p15 (446–460 BRU)  
**Epitope** KEGHQMKDCTERQANF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Claverie *et al.* 1988

- One of 4 epitopes first predicted, then subsequently shown to stimulate an HLA-A2 restricted CTL line.

**HXB2 Location** p2p7p1p6 (55–70)  
**Author Location** Gag (41–56)  
**Epitope** KEGHQMKDCTERQANF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 19 patients recognized this epitope.

**HXB2 Location** p2p7p1p6 (58–69)

**Author Location** p24

**Epitope** HQMKDCNERQAN

**Subtype** B, G

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A2, A36, B45, B58, Cw3, Cw6

**Country** Nigeria

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- This previously described epitope was embedded in a B clade peptide that was recognized by T-cells from an infected person carrying subtype G Gag. The autologous epitope sequence had 2 changes, an E8T substitution and a two amino acid insertion, QG at position 10, that could impact the anchor: HQMKDC-NtRqgQAN.

**HXB2 Location** p2p7p1p6 (62–72)

**Author Location** Gag (426–436)

**Epitope** DCTERQANFLG

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 3/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p2p7p1p6 (63–71)

**Author Location** p15 (63–71)

**Epitope** CTERQANFL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*61)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** binding affinity, subtype comparisons, acute/early infection

**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN-gamma responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, CTERQANFL, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences.

**HXB2 Location** p2p7p1p6 (63–71)

**Author Location** p15 (63–71)

**Epitope** CTERQANFL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B61)

**Donor MHC** A\*0201, A11, B51, B61, Cw\*14, Cw2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** p2p7p1p6 (63–71)**Author Location****Epitope** CTERQANFL**Immunogen** HIV-1 infection, vaccine*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41**Species (MHC)** human**Donor MHC** A\*0201, A\*1101; B\*4002, B\*5101**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** vaccine-induced epitopes**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it both before and after infection.

**HXB2 Location** p2p7p1p6 (64–71)**Author Location** p15 (64–71)**Epitope** TERQANFL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*04)**Country** China**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other**Keywords** assay standardization/improvement, optimal epitope**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, TERQANFL, was detected within overlapping peptides QMKDCTERQANFLGKIW and RQANFLGKIWP-SHKGR.

**HXB2 Location** p2p7p1p6 (64–71)**Author Location****Epitope** TERQANFL**Epitope name** Gag-TL8**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*4002)**Donor MHC** A\*0201, A\*3201, B\*4002, B\*5301, Cw\*0202, Cw\*0401**Keywords** HAART, ART**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 01RCH59 was Hispanic, not on HAART, and had a viral load of 5100 and CD4 count of 349 – she also recognized AEWDRVHPV, p24(78-86), HLA-B\*4002 and KEKGGLEGL, Nef(92-100), HLA-B\*4002.
- Among HIV+ individuals who carried HLA B40, 3/5 (60%) recognized this epitope.

**HXB2 Location** p2p7p1p6 (64–71)**Author Location** p15 (64–71)**Epitope** TERQANFL**Immunogen****Species (MHC)** human (B\*4002)**Keywords** optimal epitope**References** Frahm *et al.* 2008**HXB2 Location** p2p7p1p6 (65–75)**Author Location** Gag (429–439)**Epitope** ERQANFLGKIW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Country** India**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** subtype comparisons**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p2p7p1p6 (66–74)**Author Location** (C consensus)**Epitope** RQANFLGKI**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*13)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RQANFLGKI is an optimal epitope.

**HXB2 Location** p2p7p1p6 (66–74)  
**Author Location** Gag (429–437)  
**Epitope** RQANFLGKI  
**Subtype** B, C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*13)  
**Donor MHC** A\*0301, A\*3001, B\*1301, B\*1402, Cw\*0602, Cw\*0802  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism  
**References** Honeyborne *et al.* 2007

- To determine whether HLA-B\*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B\*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B\*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.
- Mutations in this epitope, RQANFLGKI, were seen at K436R i.e. to RQANFLGRi as well as at I437VLM i.e. to RQANFLGKv, RQANFLGKI and RQANFLGKm. These C-terminii variants may compromise viral fitness by interference with protease cleavage between p7 and p1.

**HXB2 Location** p2p7p1p6 (66–74)  
**Author Location**  
**Epitope** RQANFLGKI  
**Epitope name** RI9  
**Immunogen**  
**Species (MHC)** human (B13)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B13 epitope.

**HXB2 Location** p2p7p1p6 (66–80)  
**Author Location** p15 (66–80)  
**Epitope** RQANFLGKIWPSYKG  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** T-cell Elispot  
**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment  
**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** p2p7p1p6 (66–81)  
**Author Location** p15  
**Epitope** RQANFLGKIWPSHKGR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757–68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.



- This immunodominant, frequently targeted overlapping peptide, RQANFLGKIWPSHKGR, had an overall frequency of recognition of 23.3% - 18.6% AA, 30.8% C, 31.8% H, 9.5% WI. This peptide is included in a 27 aa Gag-p15 highly reactive region to be used for vaccine design.

**HXB2 Location** p2p7p1p6 (66–81)  
**Author Location** p15  
**Epitope** RQANFLGKIWPSHKGR  
**Immunogen**  
**Species (MHC)**  
**References**

**HXB2 Location** p2p7p1p6 (70–77)  
**Author Location** p15 (70–77)  
**Epitope** FLGKIWPS  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** binding affinity, subtype comparisons, acute/early infection  
**References** Malhotra *et al.* 2007b

- T-cell responses to clade B Gag peptides were tested using sequences based on consensus (CON), most recent common ancestor (CON) and center of tree (COT); as well as CON sequences from clade A, clade C and M-group Gag. It was found that Gag-specific cross-clade T-cell IFN- $\gamma$  responses are detectable during primary infection, and there was no significant difference in breadth or magnitude of responses with the different peptide sets. While several epitopes in low diversity domains are invariant across clades, other recognized variants are seen outside HLA anchor positions. T-cell immunity often tolerates conservative or semi-conservative amino acid substitutions but changes presumed to be in TCR contact sites may abrogate epitope recognition.
- This epitope, FLGKIWPS, is invariant across CON A, B, C and M-Group sequences, as well as clade B COT and ANC sequences.

**HXB2 Location** p2p7p1p6 (70–77)  
**Author Location** Gag (433–)  
**Epitope** FLGKIWPS  
**Epitope name** Gag433  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* peptide *HIV component:* Gag  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)  
**Species (MHC)** human, transgenic mouse (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction  
**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder that induced CTL and CD8+ T-cell IFN  $\gamma$  responses in mice. Responses were detected in 7/17 HIV+ HLA-A2 subjects.

**HXB2 Location** p2p7p1p6 (70–79)  
**Author Location** Gag (433–442)  
**Epitope** FLGKIWPSHK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** United States  
**Assay type** Intracellular cytokine staining, Other  
**Keywords** rate of progression, escape, immune evasion  
**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- Two patients developed responses to epitope FLGKIWPSHK during primary infection and one after primary, during early chronic infection. This was one of the epitopes targeted by broad HLA-A2-restricted CTL responses.

**HXB2 Location** p2p7p1p6 (70–79)  
**Author Location** p15 (70–79)  
**Epitope** FLGKIWPSHK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method

of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.

- This epitope, FLGKIWPSHK, was detected within overlapping peptides QMKDCTERQANFLGKIW, RQANFLGKIWPSHKGR and GKIWPSHKGRPGNFLQSR.

**HXB2 Location** p2p7p1p6 (70–79)

**Author Location** p15 (70–79 SF2)

**Epitope** FLGKIWPSYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** immunodominance

**References** Yu *et al.* 2002b

- 26/57 HIV-1 infected subjects displayed Gag p15-specific CD8+ T-cell IFN $\gamma$  responses were measured by Elispot and intracellular staining. The immunodominant regions targeted by CD8+ T-cells were mapped to three functional domains: the zinc finger structures, the protease cleavage site p7/p1, and to the Vpr binding site in p6.
- p15 contributed on average 17% of the total Gag response (range 0–100%).
- 3 optimal CTL epitopes were mapped within p15: KELY-PLTSL, CRAPRKKGC, and FLGKIWPSYK.
- FLGKIWPSYK was embedded in a peptide recognized by 14/57 (25%) of subjects.
- 13/24 (54%) of HLA-A\*0201+ subjects recognized this peptide.

**HXB2 Location** p2p7p1p6 (70–79)

**Author Location** p2p7p1p6 (1–10)

**Epitope** FLGKIWPSYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** p2p7p1p6 (70–79)

**Author Location** (C consensus)

**Epitope** FLGKIWPSHK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** p2p7p1p6 (70–79)

**Author Location** (C consensus)

**Epitope** FLGKIWPSHK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FLGKIWPSHK is an optimal epitope.

**HXB2 Location** p2p7p1p6 (70–79)

**Author Location** (C consensus)

**Epitope** FLGKIWPSHK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FLGKIWPSHK is an optimal epitope.

**HXB2 Location** p2p7p1p6 (70–79)

**Author Location**

**Epitope** FLGKIWPSYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A02)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.

- Epitope FLGKIWPSYK elicited a magnitude of response of 200 SFC with a functional avidity of 5nM and binding affinity of 40nM.

**HXB2 Location** p2p7p1p6 (70–79)  
**Author Location** Gag (1–10)  
**Epitope** FLGKIWPSYK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** goat (A2)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding  
**Keywords** acute/early infection, optimal epitope  
**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection, in 54% of 74 chronically infected A2+ individuals, but in no acute cases (0/14).

**HXB2 Location** p2p7p1p6 (70–79)  
**Author Location** p2p7p1p6  
**Epitope** FLGKIWPSYK  
**Epitope name** A2-FK10(p1)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p2p7p1p6 (73–81)  
**Author Location** p2p7p1p6 (2113–)  
**Epitope** KIWPSYKGR  
**Epitope name** A\*3101 KR9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3101)  
**Country** Australia  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape, HLA associated polymorphism  
**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore *et al.*, *Science* 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The seventh position (K), KIWPSYkGR, is an HLA-A\*3101 correlated amino acid. The susceptible form of this epitope is KIWPSYKGR, whilst the escape form is KIWPSYrGR, as indicated by the mutational patterns; this was validated experimentally using IFN-gamma Elispot and functional avidity studies.

**HXB2 Location** p2p7p1p6 (83–97)  
**Author Location** p15 (418–433 BRU)  
**Epitope** GNFLQSRPEPTAPPF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Claverie *et al.* 1988

- One of 4 epitopes first predicted, then subsequently shown to stimulate an HLA-A2 restricted CTL line.

**HXB2 Location** p2p7p1p6 (83–97)  
**Author Location** Gag (69–83)  
**Epitope** GNFLQSRPTAPPF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 19 patients recognized this epitope.

**HXB2 Location** p2p7p1p6 (83–97)  
**Author Location** Gag (453–462 BH10, LAI)  
**Epitope** GNFLQSRPEPTAPPF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is PEP-TAPPFLQ) has similarity with the T-cell surface glycoprotein CD5, fragment PEPTAPPRLQ.

**HXB2 Location** p2p7p1p6 (85–94)  
**Author Location** Gag (448–457 Henan isolate)  
**Epitope** FLQSRPEPTA  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding  
**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.
- Newly identified HLA-A2-restricted epitope.
- FLQSRPEPTA was among 5 mostly recognized peptides (77%).

**HXB2 Location** p2p7p1p6 (91–100)  
**Author Location** p2p7p1p6  
**Epitope** EPTAPPEESF  
**Subtype** D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35, B58)  
**Donor MHC** A23, A24, B35, B58, Cw4, Cw7  
**Country** Democratic Republic of the Congo  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction  
**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p2p7p1p6 (103–120)  
**Author Location** Gag  
**Epitope** GEETTPSQKQEPIDKEL  
**Epitope name** GAG-64  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, immunodominance  
**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, gEETTtPsqKQEPiDkEl differs from the consensus C sequence EETTPapKQEPkDrEp at 7 amino acid positions, i.e. by 38.9%.

**HXB2 Location** p2p7p1p6 (108–116)  
**Author Location** p2p7p1p6  
**Epitope** TPSQKQEPI  
**Subtype** D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Donor MHC** A23, A24, B35, B58, Cw4, Cw7  
**Country** Democratic Republic of the Congo  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction  
**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p2p7p1p6 (108–116)  
**Author Location** p15  
**Epitope** TPSQKQEPI  
**Subtype** D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B53)  
**Donor MHC** A23, A34, B44, B53, Cw4, Cw6  
**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p2p7p1p6 (110–118)

**Author Location** Gag (Henan isolate)

**Epitope** SQKQEIQIDK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Gong *et al.* 2006

- CTL responses were studied in treated and untreated donors from China, using Gag peptides from Henan isolate. All peptides were predicted to have A2 or A11 restriction (two of the most prominent alleles in Chinese population) and HLA restriction was further analyzed by CTL recognition in patients carrying corresponding allele. Among treated donors, HLA-A2 donors had higher CTL response than than HLA-A11 donors. Chronically infected untreated individuals had higher magnitude of CTL response than treated ones.

**HXB2 Location** p2p7p1p6 (111–127)

**Author Location** Gag

**Epitope** QKQGTIDKELYPLASLK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A28, A29, B14, B44, Cw8

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This is a novel unmapped epitope. Two changes over time in the individual that recognized this peptide: QKQGTkDKELYP-LvSLK

**HXB2 Location** p2p7p1p6 (111–127)

**Author Location** Gag

**Epitope** QKQEPIDKELYPLASLK

**Epitope name** GAG-65

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, qKQEPIDkElyPLaSLK differs from the consensus C sequence pKQEPkDrEPLtSLK at 6 amino acid positions, i.e. by 35.3%.

**HXB2 Location** p2p7p1p6 (113–121)

**Author Location** p15

**Epitope** QEPIDKELY

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Donor MHC** A23, A34, B44, B53, Cw4, Cw6

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.

- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p2p7p1p6 (114–123)

**Author Location** (C consensus)

**Epitope** EPKDREPL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- EPKDREPL is an optimal epitope.

**HXB2 Location** p2p7p1p6 (114–123)

**Author Location** p2p7p1p6

**Epitope** EPIDKELYPL

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p2p7p1p6 (114–123)

**Author Location** p15

**Epitope** EPIDKELYPL

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Donor MHC** A23, A34, B44, B53, Cw4, Cw6

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p2p7p1p6 (118–126)

**Author Location** Gag (481–489)

**Epitope** KELYPLTSL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*40)

**Donor MHC** A\*03, A\*24, B\*35, B\*40

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, variant cross-recognition or cross-neutralization, superinfection

**References** Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- A response to this epitope was detected before superinfection but diminished afterward. The epitope in the infecting and superinfecting strain had the sequence: kelyplAsl. The second infecting strain had a 4-amino acid insertion proximal to the epitope, RGIDkelyplAsl.

**HXB2 Location** p2p7p1p6 (118–126)

**Author Location** p2p7p1p6 (118–126)

**Epitope** KELYPLTSL

**Immunogen**

**Species (MHC)** human (B\*4001)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is a B\*4001 epitope.

**HXB2 Location** p2p7p1p6 (118–126)

**Author Location** p6 (2233–)

**Epitope** KELYPLTSL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4001)

**Country** Australia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, HLA associated polymorphism

**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore *et al.*, *Science* 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The mutational patterns in the second position in the HLA B\*4001 epitope KELYPLTSL are correlated with the host carrying HLA B\*4001.

**HXB2 Location** p2p7p1p6 (118–126)**Author Location** Gag p6 (481–489)**Epitope** KELYPLTSL**Epitope name** KL9**Immunogen** HIV-1 infection**Species (MHC)** human (B40)**Donor MHC** A\*02, A\*32, B\*07, B\*40, Cw\*03, Cw\*07**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- A B40+ mother carried the KEmYPLaSL variant of the epitope and transmitted it to her B40- infant. The variant form continued to dominate the infant's sequences at months 3 and 15.

**HXB2 Location** p2p7p1p6 (118–126)**Author Location** p15**Epitope** KELYPLTSL**Epitope name** B40-KL9(p15)**Immunogen** HIV-1 infection**Species (MHC)** human (B40)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.

- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** p2p7p1p6 (118–126)**Author Location** p15 (118–126 SF2)**Epitope** KELYPLTSL**Epitope name** p15-24**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B60)**Keywords** immunodominance, cross-presentation by different HLA**References** Yu *et al.* 2002b

- 26/57 HIV-1 infected subjects displayed Gag p15-specific CD8+ T-cell IFN $\gamma$  responses were measured by Elispot and intracellular staining. The immunodominant regions targeted by CD8+ T cells were mapped to three functional domains: the zinc finger structures, the protease cleavage site p7/p1, and to the Vpr binding site in p6.
- p15 contributed on average 17% of the total Gag response (range 0-100%).
- 3 optimal CTL epitopes were mapped within p15: KELYPLTSL, CRAPRKKGC, and FLGKIWPSYK.
- Four patients who were HLA-B60+ recognized KELYPLTSL.
- The binding motif for B60 is C-term Leu and 2nd position Glu.
- Four patients who did not carry HLA-B60 also recognized the 15 amino acid long peptide carrying KELYPLTSL, suggesting other epitopes in this immediate region can be presented by other HLA class I molecules.

**HXB2 Location** p2p7p1p6 (118–135)**Author Location** Gag**Epitope** KELYPLASLKSFLGNDPS**Epitope name** GAG-66**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Country** China**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, immunodominance**References** Zhao *et al.* 2007

- 46 ART-naïve subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.

- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, kElyPLaSLKSLFGnDPs differs from the consensus C sequence rEPLtSLKSLFGsDPI at 6 amino acid positions, i.e. by 33.3%.

**HXB2 Location** p2p7p1p6 (118–137)

**Author Location** Gag

**Epitope** KEMYPLASLRSLFGNDPSSQ

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope.
- An S->L change was observed over time: KEMY-PLASLRSLFGNDPISQ

**HXB2 Location** p2p7p1p6 (120–129)

**Author Location** p2p7p1p6

**Epitope** LYPLASLRSL

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell

responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.

- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p2p7p1p6 (121–129)

**Author Location** p15

**Epitope** YPLASLRSL

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Donor MHC** A23, A34, B44, B53, Cw4, Cw6

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p2p7p1p6 (121–129)

**Author Location** p2p7p1p6 (36–44)

**Epitope** YPLASLRSL

**Epitope name** B7-YL9 Gag

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant ypPlaslrsl. The CTL response was zero at all timepoints for the first variant. Insertion of a proline at position 3 (first variant) resulted in prevention of initial presentation of this region to the immune system.

**HXB2 Location** p2p7p1p6 (121–130)

**Author Location** p2p7p1p6

**Epitope** YPLASLRSLF

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)



**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

**HXB2 Location** p2p7p1p6 (121–130)

**Author Location** Gag (484–493)

**Epitope** YPLTSLRSLF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Jin *et al.* 2000b

- This B7 epitope is one of three subdominant CTL responses detected in a long-term non-progressor.
- A dominant B7 epitope was defined using conventional methods, and three additional sub-dominant HLA B7 epitopes were defined by first using a non-anchor based strategy, EpiMatrix, to identify 2078 possible epitopes in the autologous HIV-1, followed by B7 anchor residue prediction to narrow the set to 55 peptides for experimental testing.

**HXB2 Location** p2p7p1p6 (121–130)

**Author Location** Gag

**Epitope** YPLTSLRSLF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A\*0301, A\*2301, B\*0702, B\*1503

**Country** United States

**Keywords** escape, acute/early infection

**References** Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- T to A mutation was observed in position 4, and R to K in position 7.

**HXB2 Location** p2p7p1p6 (122–132)

**Author Location** Gag (486–496)

**Epitope** PLTSLKSLFGS

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 3/25 patients responded to this peptide (IFN- $\gamma$  CD8+ response). An IL-2 response was not detectable.

**HXB2 Location** p2p7p1p6 (123–130)

**Author Location** p2p7p1p6

**Epitope** LASLRSLF

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B58)

**Donor MHC** A23, A24, B35, B58, Cw4, Cw7

**Country** Democratic Republic of the Congo

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction

**References** Geels *et al.* 2005

- Cross-clade CTL responses in 10 non-B HIV-1 infected individuals were evaluated. T-cell reactivity was tested against peptide pools of clade B Gag, Pol, Nef, Rev and Tat. Nine individuals demonstrated cross-reactive T-cell responses to clade A, B, and C Gag pools; 6/7 patients that responded to Nef-B also reacted to clade A and C Nef pools. An inverse correlation was observed between the sequence divergence of the HLA class I restricted epitopes and the height of the T-cell responses, which in Gag could be explained through variations in the HLA-anchor residues. 42% of the responses were directed to regions containing new epitopes.
- Predicted epitope based on an HLA motif embedded in a reactive peptide from a person carrying a D clade Gag.

## II-B-6 Gag CTL/CD8+ epitopes

**HXB2 Location** Gag

**Author Location**

**Epitope**

**Immunogen** computer prediction

**Species (MHC)** (A\*0201, B\*3501)

**Keywords** subtype comparisons, computational epitope prediction

**References** Schönbach *et al.* 2002

- Computational methods (artificial neural networks, hidden Markov models, binding matrices based on HLA association rates) were used to identify HLA-A\*0201 and HLA-B\*3501 HIV T-cell epitope candidates from 533 Gag, Env and Pol sequences of which 374 were derived from HIV-1, 97 were derived from HIV-2 and 62 from SIV. Comparisons to known epitopes and between clades were made.

**HXB2 Location** Gag

**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201, Cw\*08)**References** Shacklett *et al.* 2000

- HIV-1 specific, MHC class I-restricted CTL killing was detected in duodenal and rectal gut associated lymphoid tissue (GALT) sites from three infected individuals – the distribution of class I restricted CTL was different in the peripheral blood samples and GALT samples.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Assay type** Tetramer binding, Flow cytometric T-cell cytokine assay**Keywords** assay standardization/improvement**References** Wu *et al.* 2005

- A flow cytometric assay for validation of HIV-1 gag- or pol-specific- CD8/HLA-A2 T-cells was shown to be sensitive and specific, being able to detect HIV-1 CTL at the single T-cell level. An inverse correlation between HIV plasma viremia and gag- and pol-specific-CD8/HLA-A2 T-cells was observed.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*35)**Keywords** rate of progression**References** Jin *et al.* 2002

- Patients with HLA-B\*35 variants B\*3502, B\*3503, B\*3504, and B\*5301 tend to proceed to AIDS more quickly than those with B\*3501.
- Of 32 patients with HLA-B\*35 alleles CD8+ CTL responses were quantified using an intracellular cytokine staining assay – 75% had responses to Pol, 69% to Gag, 50% to Nef, and 41% to Env.
- The overall magnitude of CTL responses did not differ between those bearing B\*3501 and the others. A higher percentage of Gag responses was observed in those that had lower RNA levels that carried B\*3501, and there was a negative association with viral load and CTL activity. The data is consistent with higher levels of CTL responses contributing to protection in B\*3501 individuals, but not in B\*3502, B\*3503, B\*3504, and B\*5301 individuals.

**HXB2 Location** Gag**Author Location****Epitope****Subtype** A, B, C**Immunogen** vaccine

**Vector/Type:** canarypox prime with gp120 boost, canarypox prime with gp160 boost  
**Strain:** B clade LAI, B clade MN, B clade SF2  
**HIV component:** Gag, gp120, gp41, Nef, Pol

**Species (MHC)** human (B60)**Keywords** subtype comparisons, vaccine-specific epitope characteristics**References** Ferrari *et al.* 2001

- Different HIV strains were used for different regions: gp41 LAI, Gag LAI, gp120 MN, gp120 SF2
- HLA-B60 responses dominated the responses against an Gag vaccine in an individual (022G0Z) who was HLA A1, A11, B8, B60. The strongest response was against the MN peptide 107-136. Low level Gag responses were observed against B8 and A11 epitopes, no response was observed against A1 epitopes.
- Vaccinee 202T7 (HLA A2, B27, C25) made the strongest response to an epitope at positions 131-140 of Gag. The response was highly cross-reactive with D clade Gag expressed from vaccinia, less so with C, and only minimally cross-reactive with A and CRF01.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** vaccine

**Vector/Type:** DNA  
**HIV component:** p17/p24 Gag

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>, H-2<sup>k</sup>)**References** Iroegbu *et al.* 2000

- The p24 sequence is more conserved than is p17 within patient, and nonsynonymous substitutions are spread evenly throughout its coding regions, not concentrated in CTL epitopes.
- Minor changes in p24 did not alter the immunogenicity in H-2b,d, or k mice, while changes in p17 (92% similarity) did alter immunogenicity.

**HXB2 Location** Gag**Author Location** Gag (SF2)**Epitope****Immunogen** vaccine

**Vector/Type:** DNA, vaccinia  
**Strain:** B clade SF2  
**HIV component:** Gag, Pol

**Species (MHC)** mouse (H-2<sup>bxd</sup>)**References** Otten *et al.* 2000

- CB6F1 were primed with gag DNA by im injection and challenged with vaccinia expressing Gag/Pol (rVVgag-pol)
- Gag-specific CTL responses were detected by IFN $\gamma$  secretion in the spleen, independent of the route (intraperitoneal, intranasal or intrarectal) of rVV gag-pol challenge.
- The gag DNA vaccine induced CTL responses in 4/4 monkeys 2 weeks post immunization, but antibody responses were detected in only 1/4 monkeys after 3 immunizations.
- CTL cross-reactivity against Gag sequences 1-80, 254-323, and 421-496 was observed, suggesting multiple CTL epitope recognition.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** vaccine

**Vector/Type:** DNA  
**HIV component:** Gag

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Qiu *et al.* 2000

- Mice were injected with plasmid DNA at 0, 2 and 4 weeks and lymphocyte proliferation was measured after 6 weeks with recombinant p24 protein.
- Secreted HIV-1 Gag expression vectors generated a stronger response than standard Gag or cytoplasmic Gag expression vectors.
- IFN-gamma levels were increased compared to an undetectable IL-4 response.
- CTL levels were also increased in secreted Gag expression vaccination studies.

**HXB2 Location** Gag**Author Location** Gag (SF2)**Epitope****Immunogen** vaccine*Vector/Type:* vaccinia *Strain:* B clade SF2  
*HIV component:* Gag, Protease**Species (MHC)** macaque, mouse (H-2<sup>d</sup>)**References** zur Megede *et al.* 2000

- Sequence-modified Rev-independent gag and gag-protease gene constructs lead to increased expression levels and elevated CTL and antibody immunogenicity in BALB/c and CB6F1 mice.
- A CTL response in mice could be detected after a single immunization with codon-optimized gag, using 2 ng of plasmid; wild type gag required 200 ng to detect a response.
- Recognition of 3 different Gag peptide pools was observed, indicating a polyclonal CTL response.
- Significant gag-specific CTL responses were detected in 4/4 rhesus monkeys, in contrast to 1/4 using wildtype gag.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** vaccine*Vector/Type:* coxsackievirus *HIV component:* p24 Gag**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Halim *et al.* 2000

- An avirulent recombinant coxsackievirus (CB4-P) construct was generated that can express p24 Gag sequences – CB4-P is attenuated even in immunodeficient mice and T help responses can be elicited from peptides embedded in a surface loop of the VP1 capsid.
- This paper describes the vaccine strategy and generation of constructs, and employs amino-terminal fusion of Gag sequences to the viral polyprotein with subsequent cleavage to elicit CTL responses via MHC class I presentation in BALB/c mice.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade HXB2, B clade NL43 *HIV component:* Gag, Pol**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Huang *et al.* 2001

- Different HIV strains were used for different regions: gag HXB2, pol NL43
- Mice were immunized with four humanized DNA constructs: GagPol, that would form a pseudoparticle carrying Gag and Pol, Gag, Pol or a GagPol fusion construct.
- The GagPol pseudoparticle, Gag and GagPol fusion construct all elicited strong anti-Gag CTL, but only the GagPol fusion construct elicited strong anti-Pol CTL.

**HXB2 Location** Gag**Author Location** Gag (HXB)**Epitope****Immunogen** vaccine*Vector/Type:* Listeria monocytogenes  
*Strain:* B clade HXB2 *HIV component:* Gag**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)**Keywords** Th1**References** Mata *et al.* 2001

- BALB/c and C57BL/6 mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways.
- CD4+ Th1 T-cells mediated the Gag specific immunological protection in mice immunized with Lm-Gag and challenged with vaccinia-Gag.
- Gag-specific CTL may enhance viral clearance via IFN-gamma secretion, but are not essential for immunity.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** vaccine*Vector/Type:* Listeria monocytogenes  
*Strain:* B clade HXB2 *HIV component:* Gag**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)**Keywords** review, Th1**References** Mata & Paterson 2000

- BALB/c and C57BL/6 mice were immunized with recombinant Listeria monocytogenes (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag.
- L. monocytogenes is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm – secreted L. monocytogenes antigens are processed and presented by both class I and class II pathways.
- This article is a review of L. monocytogenes biology and its potential as a vaccine vector for HIV, comparing to other vector systems, and discussing CD4+ Th1 T-cells mediated Gag specific immunological protection in mice and the Gag CTL response.

**HXB2 Location** Gag**Author Location** Gag (IIIB)**Epitope**

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP) *HIV component:* Gag

**Species (MHC)** macaque**References** Paliard *et al.* 2000

- CTLs primed by HIV-1 p55 gag virus-like particle (VLP) vaccination recognized epitopes in four different 20 amino acid peptides p17/4, p17/8, p24/13 and p14/9.
- Cytotoxic T cell response lasted greater than 8.5 months.

**HXB2 Location** Gag**Author Location** Gag (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human

**Keywords** rate of progression, Th1

**References** Wasik *et al.* 2000

- HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of beta-chemokines and IL-2 relative to other HIV+ infants.
- HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors.
- CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccina/HIV constructs.

**HXB2 Location** Gag**Author Location** Gag (LAI)**Epitope****Subtype** B**Immunogen** vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp41, Protease, V3

**Species (MHC)** human**References** Salmon-Ceron *et al.* 1999

- The vaccine used was a rec canarypox with HIV-1 gp120 MN, tm/gag/protease LAI (vCP205), alone or with p24E-V3 MN synthetic peptide (CLTB-36)
- Twenty HIV negative subjects were vaccinated in phase I trial with combinations of vCP205 and CLTB-36.
- Immunization with vCP205 induced HIV-1-specific ABs to gp120, V3, and p24 antigens, and CTL immune responses against vCP205 were detected after the fourth immunization in 33% of the subjects against Env, Gag and Pol, but the CLTB-36 peptide did not produce AB or CTL immune responses against p24 or gp160.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP) *HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human**References** Klein *et al.* 1997

- Immunization of HIV+ people with an HIV-1 p17/p24 Ty virus-like particle (p24-VLP) resulted in a marginal, short-lived increased proliferative response to p24 and p17 and a transient elevation in viral load.

- Two of four subjects that received 500 or 1000 µg of p24-VLP had an increase in gag-specific CTL.

**HXB2 Location** Gag**Author Location** p24 (SF2)**Epitope****Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade SF2 *HIV component:* gp120, p24 Gag *Adjuvant:* MF59, PLG

**Species (MHC)** mouse, baboon**References** O'Hagan *et al.* 2000

- PLG (Polylactide co-glycolide polymer) microparticles administered in MF59 emulsion induced gp120 Ab responses and CTL immune responses against p24 gag.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Lubaki *et al.* 1999

- Three strategies were used to analyze CTL activity: area under the net HIV-specific lysis curve (ACU), linear regression (LR) of net specific lysis, and the standard method, lytic units (LU20)
- A correlation between low HIV plasma viral load and increased levels of HIV-specific Gag and Nef CTL activity was observed using ACU and LR, but not LU20.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Kalams *et al.* 1999a

- The presence of HIV-1 p24-specific proliferative responses was positively correlated with Gag-specific memory CTL and negatively correlated with viral load in untreated subjects.
- Gag proliferative responses were the most readily detected – Gag CTL responses were the only responses with a significant correlation with Gag stimulated help, although there was a positive trend with Nef, Env and RT.

**HXB2 Location** Gag**Author Location** p55 (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Greenough *et al.* 1999

- 7/128 HIV-1 infected hemophiliac were identified as long-term non-progressors (LTNPs) and were monitored for viral and host immune parameters over 15 years – LTNPs maintained a low viral load, high frequencies of CTL precursors directed against Gag antigen and low levels of HIV-specific effector CTL activity – effector cell activity suggests low level ongoing viral replication.

**HXB2 Location** Gag**Author Location** Gag

**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Trickett *et al.* 1998

- Twelve HIV-1 infected patients were re-infused with their own lymphocytes, cryopreserved from an earlier time point in the infection.
- Improvement in CD4+ and CD8+ T cells was seen in 7/12, and an increase in the CTL response to Gag was seen in one patient.

**HXB2 Location** Gag**Author Location** Gag (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression**References** Betts *et al.* 1999

- This study demonstrated an inverse correlation between HIV Type I plasma viral load and CTL activity directed against HIV-1 Pol, and stronger combined effects of Pol- and Env-specific CTL, in long-term survivors (LTS) of HIV-1 infection.

**HXB2 Location** Gag**Author Location** Gag (LAI)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Legrand *et al.* 1997

- Seventeen recently infected patients were tested for CTL response to HIV proteins Env, Gag, Pol, Rev, Nef, Vif and Tat.
- An early response (within a month following PI) was noted in 87% of the subjects to Gag, 75% to Env, and 50% to Nef.
- Early responses to Pol, Rev, Vif and Tat were rare.

**HXB2 Location** Gag**Author Location** Gag (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Betts *et al.* 1997

- 6/8 individuals from Zambia infected with C clade virus had CTL that were able to make response to B clade HIV-1 IIIB vaccinia-expressed Gag, Pol and Env proteins.
- A vigorous cross-clade response was not limited to a particular protein, and the level of recognition of different proteins varied among the six patients.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** De Maria *et al.* 1997

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T cell function.

- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels.

**HXB2 Location** Gag**Author Location** Gag (LAI)**Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Protease**Species (MHC)** human**References** Belshe *et al.* 1998

- The live canarypox vaccine ALVAC-HIV(vCP205) carrying MN gp120, LAI gp41, Gag and Protease, and boosted with SF-2 rpg120, was given to HIV-1 seronegative volunteers – HIV-specific Env or Gag CD8+ CTL were detected in 64% of the volunteers.

**HXB2 Location** Gag**Author Location** Gag (LAI)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Buseyne *et al.* 1998a

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load.

**HXB2 Location** Gag**Author Location** Gag (LAI)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Buseyne *et al.* 1998b

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 exposed seronegative**Species (MHC)** human**References** Goh *et al.* 1999

- 13/37 exposed uninfected individuals with repeated high-risk sexual exposure had HIV-1 specific CTL against Env, Gag, Pol, or a combination of proteins – CTL activity was correlated with a CCR5 wildtype genotype.
- In this group, the highest CTLp frequencies were directed at Gag, but the most common response was to Env and four individuals had responses to multiple HIV-1 proteins.

**HXB2 Location** Gag  
**Author Location** Gag (LAI)  
**Epitope**  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* canarypox *HIV component:* Gag, gp120, gp41, Nef, Protease, RT  
**Species (MHC)** human  
**References** Evans *et al.* 1999

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination.

**HXB2 Location** Gag  
**Author Location** p17  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** epitope processing  
**References** Kuiken *et al.* 1999

- A correlation between conserved regions of p17 or Nef and CTL epitope density was noted. The authors suggest that this may be due to a biological reason such as epitope processing, or may be an artifact of experimental strategy for epitope definition, such that conserved epitopes would tend to be identified because they are more likely to be cross-reactive with the test reagents.
- In contrast to p17 and Nef, p24 is a more conserved protein, and known epitopes are evenly distributed across p24.

**HXB2 Location** Gag  
**Author Location** Gag (LAI)  
**Epitope**  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with vaccinia boost  
*Strain:* B clade LAI *HIV component:* Env, Gag  
**Species (MHC)** macaque  
**Keywords** Th1, Th2  
**References** Kent *et al.* 1998

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T cell immunity than either vaccine alone.
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env. The T help response happened despite a fall in antibody titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced.

**HXB2 Location** Gag  
**Author Location** Gag/Pol (LAI, MN)  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease  
**Species (MHC)** human

**References** Salmon-Ceron *et al.* 1999

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy, uninfected volunteers.

**HXB2 Location** Gag  
**Author Location** Gag/Pol (MN)  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86  
**Species (MHC)** chimpanzee  
**References** Kim *et al.* 1998

- The study explores the use of co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

**HXB2 Location** Gag  
**Author Location** Gag (BRU)  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** rate of progression  
**References** Aladdin *et al.* 1999

- *In vitro* measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death.

**HXB2 Location** Gag  
**Author Location** p24 (C consensus)  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons, immunodominance  
**References** Goulder *et al.* 2000a

- The CTL-dominant response was focused on this epitope in a HIV+ South African – this epitope did not fall within the five most recognized peptides in the study.
- Three peptides GSEELRSLYNTVATL (p17 residues 71-85), SALSEGATPQDLNNTMLNTVG (p24 41-60), and WEKIRLRPGGKKKYK (p17 16-30) contained the dominant Gag-specific epitope in 31 out of 44 B-clade infected individuals from Boston who showed Gag-CTL responses.
- Five peptides RLRPGGKKHYMIKHLVW (p17 20-36), ELRSLYNTVATLYCV (p17Gag 74-88), SALSEGATPQDLNNTMLNTVG (p24 41-60), FRDYVDRFFKTLRAEQA (p24 161-177), and SILDIKQGKEPFRDY (p24 149-164) contained dominant Gag-specific epitopes in 32 out of 37 C-clade infected subjects from South Africa.

**HXB2 Location** Gag  
**Author Location** Gag  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* ZF1 *HIV component:* complete genome  
**Species (MHC)** macaque

**References** Akahata *et al.* 2000

- Rhesus macaques were vaccinated by i.m. injection with naked plasmid DNA carrying an HIV-1 complete genome vaccine, strain ZF1, with a mutated zinc finger in the nucleocapsid to prevent packaging.
- Env and Gag specific CTL but no antibody responses were induced in 2/4 vaccinated monkeys (MM145 and MM153)
- 2/4 monkeys (MM146 and MM143) produced antibodies against p24 and/or gp160, but no CTL response was detected.
- PBMC from all vaccinated monkeys produced IFN-gamma, in response to HIV-1 gp160, indicating a Th response – this response was 5 times higher in MM145, the animal with the strongest CTL response.
- 4 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM145 and MM153 (with a homologous Env) decreased to near or below the detection limit.
- 6-8 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM146 and MM143 decreased near or below the detection limit.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression**References** Salerno-Goncalves *et al.* 2000

- A general test of CD8 anti-viral activity was developed based on proviral load of coculture of autologous CD8+ cells with CD4+ cells after homogeneous superinfection with NSI virus.
- Significantly decreased the CD4+ T-cell proviral loads were found in 12 HIV+ slow progressors relative to 10 rapid progressors.
- Significant CD8+ mediated cytotoxicity directed against autologous cells infected with vaccinia carrying the HIV-1 gag gene was observed in slow progressors in contrast to rapid progressors, but no correlation was found between plasma viral load in 22/22 asymptomatic HIV infected individuals.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Young *et al.* 2001

- Addition of recombinant rec human IL12 (rhIL12) to cultures increased HIV-specific lysis of HIV-Gag, Pol and gp120 vaccinia expressed antigens (11/15 tested increased lysis by > 5%) if the culture was derived from HIV+ individuals who had CD4 cells/ul > 500.
- 2/10 individuals with <200 CD4 cells/ul, and 3/10 individuals with 200-500 CD4cells/ul, had an increase of >5% upon treatment of the culture with rhIL12, so a few individuals in late stage disease had CD8 cells that maintained responsiveness to rhIL12.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection**Species (MHC)** mouse**References** de Quiros *et al.* 2000

- CB-17 SCID-Hu mice engrafted with peripheral blood mononuclear cells of four long-term nonprogressors (viral load < 50 copies/ml) displayed resistance to challenge with HIV-1 SF162, mediated by CD8+ T-cells and associated with proliferation in response to p24 – these patients did not have a higher level of HIV-1 specific immunity *in vitro*, so the mechanism is unknown.

**HXB2 Location** Gag**Author Location** Gag (subtype A, B, D)**Epitope****Subtype** A, B, D**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** White *et al.* 2001

- HIV-specific CTL activity was detected in the female reproductive tract of only 1/3 HIV-infected women who underwent a hysterectomy, although CTL could be identified in the PBMC of all three women.

**HXB2 Location** Gag**Author Location** Gag (HXB2)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Chun *et al.* 2001

- Suppression of viral replication in the resting CD4+ T-cell reservoir by autologous CD8+ T-cells via CD4+/CD8+ cell contacts was observed in long-term nonprogressors and patients undergoing antiretroviral treatment, but this activity appears to be independent of Gag-specific CTL activity.

**HXB2 Location** Gag**Author Location** Gag (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression

**References** Jin *et al.* 2000a

- The CTL precursor level (CTLp) was measured in long term non-progressors (LTNP) with low viral load using limiting dilution analysis and measuring CTL against Env Gag and Pol expressed in vaccinia in autologous targets.
- LTNPs have high memory CTL numbers and low viral load.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 exposed seronegative**Species (MHC)** human**Keywords** review, HIV exposed persistently seronegative (HEPS)**References** Rowland-Jones *et al.* 2001

- This is a review that summarizes observations about HIV-specific CTL found in the HIV-1 exposed persistently seronegative (HEPS) population.
- The CTL responses assayed by ELISPOT and by CTL precursor frequencies by limiting dilution analysis indicate that CTL in HEPS individuals tend to be of a lower magnitude than in chronic HIV-1 infections – the responses in HEPS cases are below the level of detection by tetramer assays.
- CD8+ CTL responses tend to be detectable in HEPS subjects only if they are recently exposed, and the response diminishes if exposure is reduced – it is not clear if there is a stable memory population in HEPS cases.
- CD8+ CTL responses in the HEPS population are associated with HIV-1 specific CD4+ T cell responses, assayed by proliferation assays, IL-2 secretion, and ELISPOT, and the authors consider the possibility that HIV-1-specific T-help responses improve the "quality" of the CD8+ response in HEPS individuals relative to HIV-1 infected individuals, who tend to have a poor HIV-1-specific T-help response.
- HIV-1 specific CD8+ CTL responses in HIV-1 infected individuals show reduced levels of perforin, and the T cells may not mature properly, and although similar studies have not been conducted in HEPS individuals this is considered as a possible difference in the CTL immune response in HEPS and HIV-1 infected people.

**HXB2 Location** Gag**Author Location****Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* DNA *HIV component:* Env, Gag, Pol**Species (MHC)** mouse**Keywords** review, vaccine-specific epitope characteristics**References** Nabel 2002

- Using DNA that had humanized codon usage, CTL responses to DNA vaccines containing either Gag, Pol, Gag-Pol fusion protein, or Gag-Pol pseudoparticles suggested that the greatest breadth and most potent response was to the Gag-Pol fusion protein. The Gag-Pol fusion lacks the Gag precursor protein required for viral assemble, so does not form releaseable particles; the author speculates that longer retention of the Gag-Pol protein within the cell may enhance antigen presentation.

**HXB2 Location** Gag**Author Location****Epitope****Subtype** B**Immunogen** HIV-1 exposed seronegative**Species (MHC)** human**Keywords** HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission**References** De Maria *et al.* 1994; Kuhn *et al.* 2002

- 6/24 HIV uninfected infants (ages 15-50 months) born to HIV+ mothers had HIV-1 specific CTL responses to vaccinia-expressed Nef, Gag/Pol, Env.
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Gag**Author Location****Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission**References** Aldhous *et al.* 1994; Kuhn *et al.* 2002

- Six of nine HIV vertically infected infants had HIV-1 specific CTL responses to vaccinia expressed Tat (4/6), Pol (6/6), Env (1/6), or Gag (1/6), but not all responses were detected at all time points.
- Two of eleven babies that were not infected though born to HIV+ mothers had detectable responses to Tat (1/2), Pol (2/2), Gag (1/2).
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Gag**Author Location****Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission, rate of progression**References** Kuhn *et al.* 2002; Wasik *et al.* 1999

- In HIV-infected infants HIV-specific, CTL responses were not detectable in icord blood or in PBMC collected shortly after birth and were absent or remained very low in 3 infants with a rapidly progressive disease. For those who progressed more slowly, the HIV-specific CTL activity varied.
- The two infants with high levels of Env peptide-stimulated IL-2 responses had the highest CTLp frequencies.
- Stronger responses were detected after initiation of the antiretroviral therapy.
- Two babies that were not infected though born to HIV+ mothers had detectable though low HIV-specific CTLp responses to Env (1/2), Pol (2/2), Gag (1/2) cord blood and transiently in PBMC after birth.
- Reviewed in Kuhn *et al.* [2002].



**HXB2 Location** Gag  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission  
**References** Kuhn *et al.* 2002; McFarland *et al.* 1994

- Only 9% of HIV+ infants had HIV-specific CTL against Env or Gag in unstimulated PBMC. After CD3 stimulation of PBMC, Gag and Env specific CTL were found in PBMC from 91% and 78% of HIV-infected children, respectively, with high precursor frequencies.
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Gag  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** epitope processing, escape  
**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed. p17 is much more variable than p24.

**HXB2 Location** Gag  
**Author Location** p24 (HXB)  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** epitope processing, vaccine-specific epitope characteristics  
**References** Lu *et al.* 2000a

- Bacillus anthrax lethal toxin (LFn)-HIV fusion proteins are candidate HIV vaccines that are safe in mice, and LFn-V3 region fusion proteins induce CD8 T cells in BALBc mice. LFn causes exogenous protein to be taken up and processed in a class I pathway. Expressed proteins from Gag p24 and Nef fragments cloned into the LFn expression plasmid stimulate gag-specific CD4 proliferation and CTL responses in HIV-infected donor PBMCs *in vitro*.

**HXB2 Location** Gag  
**Author Location** (HXB2)  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Edwards *et al.* 2002

- 96% (26/27) chronically infected HIV-1 infected patients elicited gamma-IFN CD8+ T-cell responses against Gag.

- Nef and/or Pol CTL responses were detected in 86% of the subjects.
- The magnitude and breadth of Gag and p24 T-cell responses correlated with absolute CD4 counts, and inversely correlated with viral load.
- Pol and Int CTL responses correlated positively with absolute CD4+ T-cell count.
- Nef and Env responses did not correlate with either CD4 counts or viral load.

**HXB2 Location** Gag  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HAART, ART, dendritic cells  
**References** Larsson *et al.* 2002b

- Autologous mature dendritic cells with rec vaccinia expressing Gag, Pol, Nef and Env could amplify CD8+ T-cell Eli-spot responses 4-38 fold in five HIV+ patients on successful HAART treatment, relative to autologous monocytes. Some weak responses could only be detected using mature dendritic cells as APCs, and this approach could be useful for detection of low frequency memory cells.

**HXB2 Location** Gag  
**Author Location** (IIIB)  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** immunotherapy  
**References** Trickett *et al.* 2002

- Conditions were optimized for ex-vivo expansion of CD8+ and CD4+ T-cells with the goal of functional T-cell production for autologous immunotherapy. 10,000-fold expansions were obtained in 14 days with optimized concentrations of IL-2, anti-CD3 and anti-CD28 coated microspheres, and decreasing amounts of serum over the first 8 days.

**HXB2 Location** Gag  
**Author Location** (IIIB)  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 and HCV co-infection  
**Species (MHC)** human  
**Keywords** rate of progression  
**References** Lauer *et al.* 2002

- HIV-1 and HCV immune responses were studied in 22 individuals who were co-infected with HIV-1 and hepatitis C virus (HCV). IFN $\gamma$  production was measured in an Elispot assay of CD8+ T-cells using targets expressing either Gag, RT, Env and Nef in a vaccinia construct, or one of seven HCV proteins.
- All 22 patients targeted at least one protein. 20/22 patients recognized RT, 17/22 patients recognized Gag, 13/22 subjects recognized Env and 11/22 patients recognized Nef. Robust CTL activity was independent of disease progression or viral load.

- Despite high HCV viral loads, very few HCV CD8+ T-cell Elispot responses were detected. In a control HCV infected person who did not have HIV-1, strong anti-HCV responses were mounted.
- HIV-specific CD4 proliferative responses were detected in 9/17 coinfecting patients, but no HCV responses were detected.

**HXB2 Location** Gag**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** responses in children**References** Luzuriaga *et al.* 1995

- 2/3 infants infected in utero had detectable HIV-1 Gag and Env specific CTL responses, one by 4 months, one by 11 months of age. Levels of the responses varied at different time point. Pol responses were not detected.
- 2/4 infants infected intrapartum had detectable responses, one note until 11 months, one not until 42 months.
- HIV-specific CTL were not detected in ten HIV- infants that were born to HIV+ mothers.

**HXB2 Location** Gag**Author Location****Epitope****Immunogen** vaccine*Vector/Type:* canarypox prime with gp120*boost Strain:* B clade LAI, B clade MN*HIV component:* Env, Gag**Species (MHC)** human**References** Gupta *et al.* 2002

- Different HIV strains were used for different regions: Gag, LAI; gp120, MN; and gp41, LAI
- A safety and immunogenicity study of a vaccine dosing schedule was studied in a trial conducted in high and low risk study subjects. There was a 76% cumulative probability of detecting a Gag or Env CTL response by day 728.

**HXB2 Location** Gag**Author Location****Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, responses in children**References** Scott *et al.* 2001

- CTL responses before and after initiation of ART were studied in 13 HIV-1 vertically infected infants <6 months of age, and 4 that were >6 months of age.
- Before ART 2/13 infants <6 months of age showed IFN $\gamma$  Elispot CD8+ T-cell responses, one to Nef and one to Env and Nef, and these responses became undetectable after successful therapy– 3 infants were coinfecting with CMV and all 3 had CMV-specific CD8+ T-cell responses.
- One older infant, at 23 months, had CTL responses against all for proteins tested, Gag, Pol, Nef and Env, and had the lowest plasma viremia of the study group. 3/4 infants older than 6 months of age responded to either Nef or Pol.

- Administration of ART over 48 weeks broadened the HIV-1-specific CTL response in 2/4 of the older children that were incomplete responders.

**HXB2 Location** Gag**Author Location** (IIIB, MN)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** dendritic cells**References** Larsson *et al.* 2002a

- Dendritic cells acquire and present HIV-1 antigens derived from dead, apoptotic cells or from non-infectious, fusion-competent HIV-1 virions, and these DC cells could stimulate CD4+ and CD8+ T-cells resulting in IFN $\gamma$  production in an Elispot assay. Both HLA Class I and class II molecules were used for presentation. This may be an important aspect of the initial immune response to HIV-1 infection of CD4+ cells in the mucosal subepithelia.

**HXB2 Location** Gag**Author Location** (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, supervised treatment interruptions (STI)**References** Ortiz *et al.* 2001

- Immune responses in eight chronically HIV-1 infected patients undergoing HAART therapy structured treatment interruptions (STI) were studied. STI boosted HIV-1 specific CTL responses and elevated CTL responses were maintained up to 22 weeks after the last treatment interruption, but viral load rebound to pretreatment levels and CD4 T-cell count decline was observed. CD8 responses in PBMC were measured by cytokine flow cytometry with gp160, Gag p55, RT-Pol and Nef expressed in vaccinia.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Subtype** AG, B**Immunogen****Species (MHC)** human**References****HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen****Species (MHC)** human**References****HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** Intracellular cytokine staining

**Keywords** HAART, ART, computational epitope prediction, supervised treatment interruptions (STI)

**References** Amicosante *et al.* 2002

- A new assay was developed to detect CTL responses to HIV using 28 pooled 15-mer peptides from conserved regions in Gag that were selected to be rich in HLA class I motifs, carrying potential epitopes for more than 90% of HLA class I haplotypes, and to be conserved between subtypes. Some peptide variants were included, expanding the potential for cross-clade recognition. 12 Caucasians, even those on successful HAART, had detectable CTL responses using this assay, and as did five Africans. People with either B subtype or A-G recombinant infections all reacted.
- The Gag peptide ICS assay was more sensitive to picking up CTL reactivity than whole Gag in HAART treated people. Initiation of STI increased the number of IFN-gamma producing CD8+ T-cells detected using the peptide assay.

**HXB2 Location** Gag

**Author Location** Gag

**Epitope**

**Immunogen** vaccine

*Vector/Type:* vaccinia *HIV component:* Gag *Adjuvant:* block copolymer CRL8623

**Species (MHC)** macaque

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** vaccine-induced epitopes

**References** Caulfield *et al.* 2002

- Codon-optimized HIV Gag DNA vaccines were given i.m. with or without a nonionic block copolymer(CRL8623) as adjuvant. DNA-CRL8623 formulations induced 2-fold higher Elispot responses, shifting the response towards CD8+ T-cells.
- 23 monkeys recognized 25 different epitopes with an average of 2.7 epitopes per monkey, and a minimum of 1 and a maximum of 5 peptides per monkey.
- Responses were detected up to 18 months after vaccination.

**HXB2 Location** Gag

**Author Location** Gag

**Epitope**

**Subtype** multiple

**Immunogen**

**Species (MHC)** human

**Assay type** Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Currier *et al.* 2003

- CD8-cellular immune responses from 21 HIV-1 infected patients from Kenya infected with subtype A, C, D, and unique recombinants were studied for cross-recognition of Gag, Env, and Nef vaccinia-expressed proteins representing subtypes A-H, including CRF01.
- Both subtype-specific and cross-reactive CTL were observed, with a skewing of responses towards the infecting subtype in the nine subjects with full length sequence available. The magnitude of the responses to Gag were the highest, less to Nef, and still less to Env.

- For Gag, 8/21 subjects responded to at least 7/8 different subtype proteins, 7 had a mixed response, recognizing some subtypes but not others, and 6 responded to only one or none of the different subtype proteins. For Env, 4/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 7 responded to one or none. For Nef, 5/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 6 responded to one or none.

**HXB2 Location** Gag

**Author Location** Gag (SF2)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, protein, virus-like particle (VLP), PLG microparticle *Strain:* B clade SF2 *HIV component:* Gag *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72), LTK63

**Species (MHC)** macaque

**Assay type** proliferation, Chromium-release assay

**References** Otten *et al.* 2003

- Immunization strategies for Gag (p55) in macaques were compared. GAG DNA prime with a boost of Gag adsorbed onto PLG (polyactide coglycolide) microparticles with LTK63 as adjuvant gave the strongest CD4+ T cell proliferative, CTL, and antibody responses, compared with Gag protein, or Gag virus-like particles (VLP). GAG DNA was best for inducing CTL responses, Gag-PLG for T-help and antibody; the prime-boost combination gave strong responses for all three.

**HXB2 Location** Gag

**Author Location** Gag

**Epitope**

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, acute/early infection, early-expressed proteins

**References** Masemola *et al.* 2004a

- Anti-HIV T-cell responses in subtype C HIV-1 infected individuals in the beginning of the infection target multiple protein regions, but the responses are dominated by Nef, making up almost one-third of the total responses; the second most targeted protein was p24. A correlation between Gag specific responses and plasma viral load was also found.
- Neither breadth nor magnitude of CD8+ T-cell responses were correlated with control of virus, however hierarchical preferential targeting of Gag was significantly associated with lower viral loads.

**HXB2 Location** Gag

**Author Location** Gag

**Epitope**

**Subtype** A

**Immunogen** vaccine

*Vector/Type:* DNA, modified vaccinia Ankara (MVA), polyepitope, DNA prime with modified vaccinia Ankara (MVA) boost  
*Strain:* A clade *HIV component:* p17/p24 Gag

**Species (MHC)** human

**Country** United Kingdom

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** epitope processing, vaccine-induced epitopes, vaccine antigen design

**References** Mwau *et al.* 2004

- Phase I clinical trial in healthy uninfected individuals was conducted evaluating the immunogenicities of candidate DNA- and MVA-vectored HIV vaccines. Both DNA and MVA vaccines alone and combined (DNA prime-MVA boost) were shown to be safe and induce HIV-specific responses in 78%, 88% and 89% of individuals, respectively. Responses in some individuals could be detected 1 year after vaccination.
- The vaccine in this case was a clade A p17/p24 antigen linked to a polyepitope string of A clade epitopes. Responses were tested with peptide pools, and multiple strong responses to the gag proteins and to the polyepitope region were observed. MVA alone did as well as a DNA prime, MVA boost in this study, although the study included small numbers.

**HXB2 Location** Gag

**Author Location** Gag

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* non-replicating adenovirus  
*Strain:* B clade *HIV component:* Gag

**Species (MHC)** mouse

**Assay type** Intracellular cytokine staining

**Keywords** Th1, Th2

**References** Pinto *et al.* 2003

- Heterologous prime boosts with replication-defective adenoviral vectors of different simian serotypes expressing the same transgene product of HIV-1 were shown to be highly efficient in increasing specific CD8+ T-cell responses.

**HXB2 Location** Gag

**Author Location**

**Epitope**

**Subtype** CRF02\_AG

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP), DNA prime with modified vaccinia Ankara (MVA) boost  
*Strain:* CRF02 IC0928 *HIV component:* Env, Gag, Pol

**Species (MHC)** macaque

**Assay type** T-cell Elispot, Intracellular cytokine staining

**Keywords** vaccine-specific epitope characteristics, vaccine antigen design

**References** Ellenberger *et al.* 2005

- Macaques were given a Gag-Pol-Env DNA prime followed by an MVA boost. Two DNA constructs were compared, one that resulted in mature VLPs with processed Gag (IC48) and one that had a point mutation in Gag that resulted in immature VLPs (IC1-90). IC48 DNA vaccinations, which produced

mature VLPs, yielded 2-fold stronger T-cell responses with greater breadth. CD4 T-cells responded to 3-fold more peptide pools than did CD8.

**HXB2 Location** Gag

**Author Location** Gag

**Epitope**

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** South Africa

**Assay type** Flow cytometric T-cell cytokine assay

**Keywords** characterizing CD8+ T cells

**References** Ramduth *et al.* 2005

- The magnitude of HIV-specific CD8 responses in HIV-1 infected individuals from South Africa correlated with the CD4 responses. CD4 responses were much more narrowly focused, with Gag as dominant target, while CD8 responses were equally distributed among Gag, Pol and the regulatory and accessory proteins. An association between the preferential targeting of Gag by CD8 T-cells and viral control was found.

**HXB2 Location** Gag

**Author Location** Gag (Consensus B, DU422)

**Epitope**

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** assay standardization/improvement, subtype comparisons, variant cross-recognition or cross-neutralization

**References** Sabado *et al.* 2005

- CD8 T-cell responses were tested in HIV-1 clade B infected individuals using Gag peptides based on clade B consensus sequence and clade C primary isolate DU422. Peptides from both clades were shown to be of equal sensitivity, with equal numbers of discordantly detected responses. The majority of discordant detection was due to sequence differences between clades. Thus, clade B consensus peptides were not superior in detecting CD8 T-cell responses in clade B-infected individuals.

**HXB2 Location** Gag

**Author Location** Gag

**Epitope**

**Subtype** A, B, C, M

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States, Zambia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

**References** Bansal *et al.* 2006

- This study compared T-cell reactivity to consensus A, B, C, M, ancestral B, M and HXB2 15-mer overlapping peptides in patients from US (subtype B) and Zambia (subtype C).

- Broad cross reactivity was demonstrated. Consensus M, B, ancestral B and HXB2 elicited similar levels of responses in US patients. Consensus C, M and ancestral M elicited similar levels of responses in Zambia patients.

**HXB2 Location** Gag

**Author Location**

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost, DNA, Other *Strain:* Other *HIV component:* Env, Gag

**Species (MHC)** mouse

**Assay type** T-cell Elispot

**Keywords** vaccine-induced epitopes, vaccine antigen design

**References** Xu *et al.* 2006

- Sequential cross-clade vaccination strategy was tested in BALB/c and C57BL/6 mice. Vaccines used were C/B recombinant strain (CN54), B strain (RL42), A/E recombinant strain (AE2F).
- Sequential priming and boosting with heterologous HIV immunogens stimulated T cell immunity against conserved epitopes, while a single vaccine derived from one clade or the mixture of multiple vaccines from different clades raised T cells against less conservative or non-conservative epitopes.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** T-cell Elispot

**References** Wang *et al.* 2006

- The association between T cell response and CD4+ T cell counts or CD4+ was investigated, using overlapping peptides corresponding to natural B clade and C consensus sequences.
- T cell responses and CD4+ count were correlated for Gag p24 and Gag p17 (B and C clades) and for Pol (C clade). CD4+ counts were higher in patients with Tat and /or Rev T cell response than in patients without Tat and Rev response.

**HXB2 Location** Gag

**Author Location** p17

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** T-cell Elispot

**References** Wang *et al.* 2006

- The association between T cell response and CD4+ T cell counts or CD4+ was investigated, using overlapping peptides corresponding to natural B clade and C consensus sequences.
- T cell responses and CD4+ count were correlated for Gag p24 and Gag p17 (B and C clades) and for Pol (C clade). CD4+ counts were higher in patients with Tat and /or Rev T cell response than in patients without Tat and Rev response.

**HXB2 Location** Gag

**Author Location** Gag (HXB2)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Jiao *et al.* 2006

- CD8+ responses were compared in long-term nonprogressors, asymptomatic progressors and progressors. There were no significant differences among 3 cohorts. However, CD8 responses and CD4 counts in asymptomatic progressors, as well as CD4 responses and viral loads in progressors were inversely correlated. In addition, in 6 long-term nonprogressors, a quick loss of CD4 T-cells was associated with simultaneous vigorous CD8 responses.

**HXB2 Location** Gag

**Author Location**

**Epitope**

**Immunogen** vaccine

*Vector/Type:* adenovirus type 5 (Ad5) *HIV component:* Env, Gag *Adjuvant:* Cholera toxin (CT)

**Species (MHC)** macaque

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** vaccine antigen design

**References** Mercier *et al.* 2007

- 3 rhesus macaques were given oral immunizations with an enteric-coated mixture of adenoviral vectors expressing HIV-1 gag and a string of conserved env peptides representing broadly cross-reactive CD4+ and CD8+ epitopes. The macaques were boosted intranasally with a mixture of 6 HIV-1 envelope peptides plus cholera toxin adjuvant.
- The immunizations increased cellular immune responses, including antigen-specific IFN $\gamma$ -producing CD4+ and CD8+ effector memory T cells in the intestine. After only the oral immunization, there were no EliSpot responses to env peptides or to gag. After the intranasal boost, EliSpot responses against env peptides and against inactivated HIV were markedly increased, but gag responses were not.

**HXB2 Location** Gag

**Author Location** Gag (HXB2)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost *Strain:* B clade HXB2 *HIV component:* Gag

**Species (MHC)** mouse

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** vaccine-induced epitopes, Th1

**References** Arruda *et al.* 2006

- p55 Gag cellular trafficking of two chimeras (DNA plasmid with either lysosomal-associated membrane protein LAMP/gag or human dendritic cell CD-LAMP/gag) was studied in mice. Both produces potent T and B cell immune responses, but DC-LAMP produces stronger Th1 response. The chimeras produces also significant responses to cryptic epitopes that were not recognized after immunization with native gag DNA.

**HXB2 Location** Gag

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade

**Species (MHC)** macaque

**Assay type** Intracellular cytokine staining

**Keywords** subtype comparisons, vaccine antigen design

**References** Smith *et al.* 2005

- Macaques were immunized with a clade B HIV vaccine and tested for responses to pools of clade B and A/G Env and Gag peptides. While CD4 responses were more frequent than CD8 responses, higher cross-clade responses were found for CD8 responses. The authors suggest that the better cross-clade reactivity of the CD8 responses reflects the size difference between CD8 and CD4 epitopes; the smaller CD8 epitopes provide a smaller target for mutation.
- For both B and A/G Env and Gag peptides, 3/5 pools produced CD8+ T cells, suggesting the existence of 2 or 3 cross-reactive CD8 epitopes.

## II-B-7 Gag/Pol CTL/CD8+ epitopes

**HXB2 Location** Gag/Pol

**Author Location** Gag/Pol (ARV-2 SF2)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* fowlpoxvirus *Strain:* B clade ARV-2, B clade SF2 *HIV component:* Gag, Pol *Adjuvant:* IFN $\gamma$

**Species (MHC)** macaque

**References** Kent *et al.* 2000

- Vaccination with FPV Gag/Pol-IFN-gamma increased HIV-1 specific CTL and T cell proliferative responses to Gag/Pol antigens, respectively, in infected *Macaca nemestrina*.
- HIV-1 viral loads remained low and unchanged following vaccinations.

**HXB2 Location** Gag/Pol

**Author Location** RT

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12

**Species (MHC)** mouse

**References** Kim *et al.* 1997d

- A Gag/Pol or Env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules CD86, gave a dramatic increase in both the cytotoxic and proliferative responses in mice.
- When CD86 was present, CTL response could be detected even without *in vitro* stimulation.

**HXB2 Location** Gag/Pol

**Author Location** RT

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** TCR usage

**References** Gamberg *et al.* 1999

- 13/13 subjects with advanced HIV infections showed CD8 T cell proliferation and differentiation of CTL *in vitro*, and six individuals showed HIV-specific responses to Gag, Pol, Env or Nef antigens.
- Data suggests that the functional and genetic integrity of the CD8 T cell repertoire (TCR V $\beta$  gene intrafamily genetic diversity) remains intact through advanced HIV infection, although HIV-specific CTL activity decreases.

**HXB2 Location** Gag/Pol

**Author Location**

**Epitope**

**Immunogen** vaccine

*Vector/Type:* adenovirus *HIV component:* Gag-Pol, Nef, Vpr

**Species (MHC)** mouse

**References** Muthumani *et al.* 2002

- Vpr can cause cells to go into G2 arrest, and it suppresses immune cell activation and inflammatory cytokine production, so co-immunization of BALB/c mice with recombinant adenovirus expressing Vpr and HIV-1 antigens Nef or Gag/Pol was tested to see if Vpr reduced the immune response to the other HIV antigens.
- Vpr compromised CD8+ T-cell lytic responses and T-helper proliferative responses in mice co-immunized with Vpr and Nef or Gag/Pol.
- *In vitro*, Vpr reduced T-cell cytokine production of IL-12 and TNF $\alpha$ , indicative of Vpr-mediated immune suppression.

## II-B-8 Gag/Pol TF CTL/CD8+ epitopes

**HXB2 Location** Gag/Pol TF (24–31)

**Author Location**

**Epitope** NSPTRREL

**Epitope name** NL8

**Immunogen**

**Species (MHC)** human (Cw\*0102)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a Cw\*0102 epitope.

**HXB2 Location** Gag/Pol TF (24–31)

**Author Location** p6 (35–42 HXB2)

**Epitope** NSPTRREL

**Epitope name** NL8

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0102)**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape, immune evasion, optimal epitope**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Position 4 in the epitope had potentially experienced positive selection. NspTRREL and tSPTRREL escape variants were found.

**HXB2 Location** Gag/Pol TF (44–52)**Author Location** Pol (C-96BW15C05)**Epitope** AGAERQGTL**Epitope name** C**Subtype** C**Immunogen** vaccine*Vector/Type:* DNA, alphavirus replicon*Strain:* C clade C-96BW04.09, C clade C-96BW15C05 *HIV component:* Gag, Gag-Pol, Pol**Species (MHC)** mouse (H-2d)**Assay type** Flow cytometric T-cell cytokine assay**Keywords** vaccine-induced epitopes, vaccine antigen design**References** Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- This is a novel epitope.

**II-B-9 Gag/Pol TF-Protease CTL/CD8+ epitopes****HXB2 Location** Gag/Pol TF-Protease (54–6)**Author Location** Pol**Epitope** FSFPQITLW**Epitope name** FW9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A11, A2, B18, B44, Cw12, Cw5**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- An escape mutation at position 2, fNfpqitlw, was found in the most polymorphic residue in the epitope. This is a novel partially mapped epitope.

**II-B-10 Protease CTL/CD8+ epitopes****HXB2 Location** Protease (2–19)**Author Location** (C consensus)**Epitope** QITLWQRPLVSIKVGQI**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0801)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Protease (3–11)**Author Location** RT (71–79 subtype A, B, D)**Epitope** ITLWQRPLV**Subtype** A, B, D**Immunogen****Species (MHC)** human (A\*6802)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*6802 epitope.

**HXB2 Location** Protease (3–11)**Author Location** Pol**Epitope** ITLWQRPLV**Subtype** A, B, C, D**Immunogen** HIV-1 infection, vaccine*Vector/Type:* DNA prime with modified vac-*cinia Ankara (MVA) boost* *Strain:* A clade*HIV component:* p17 Gag, p24 Gag**Species (MHC)** human (A\*6802)**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polypeptide string of conserved, often immunodominant epitopes that were selected to

have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].

- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  ELISPOT assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** Protease (3–11)

**Author Location** Protease (71–79 LAI)

**Epitope** ITLWQRPLV

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*6802, A\*7401, A19)

**Keywords** subtype comparisons

**References** Dong 1998

- Predicted on binding motif, no truncations analyzed.
- Clade A/B/D consensus, S. Rowland-Jones, pers. comm.

**HXB2 Location** Protease (3–11)

**Author Location** RT (71–79 subtype A, B, D)

**Epitope** ITLWQRPLV

**Subtype** A, B, D

**Immunogen**

**Species (MHC)** human (A\*7401)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*7401 epitope.

**HXB2 Location** Protease (3–11)

**Author Location** Pol (59–)

**Epitope** ITLWQRPLV

**Epitope name** Pol59

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* Protease *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** transgenic mouse (A2)

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder, and induced CTL and CD8+ T-cell IFN  $\gamma$  responses in mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

**HXB2 Location** Protease (3–11)

**Author Location** Pol (59–65)

**Epitope** ITLWQRPLV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A28)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** Protease (3–11)

**Author Location** Pol (60–68)

**Epitope** ITLWQRPLV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A28)

**Donor MHC** A28, A29, B14, B44, Cw8

**Country** United States

**Assay type** CD8 T-cell ELISPOT - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Protease (3–11)

**Author Location** RT (71–79 LAI)

**Epitope** ITLWQRPLV

**Epitope name** P2

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A28 supertype)

**Keywords** HAART, ART, supertype

**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** Protease (3–11)

**Author Location** Pol

**Epitope** ITLWQRPLV

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A74)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ITLWQRPLV cross-reacts with clades A, B and D.



- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** Protease (4–14)

**Author Location** Pol (60–70 SF2)

**Epitope** TLWQRPLVTIR

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (A\*3303)

**Assay type** Chromium-release assay

**Keywords** binding affinity, computational epitope prediction

**References** Hossain *et al.* 2003

- HLA-A\*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A\*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A\*3303. Six of these served as peptide-targets for lysis by PBMC from infected individual, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
- This epitope is one of the 4 that are properly processed.

**HXB2 Location** Protease (7–15)

**Author Location** Protease

**Epitope** QRPLVTIKI

**Epitope name** QI9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0101)

**Donor MHC** A\*0101, A\*0205, B\*0702, B\*0801, Cw\*0701, Cw\*0702

**Country** Australia

**Assay type** Intracellular cytokine staining

**Keywords** HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization, optimal epitope

**References** Stratov *et al.* 2005

- CD8 T-cells targeting epitopes spanning drug resistance induced mutations were detected in 3/25 individuals harboring multidrug-resistant HIV-1. Novel CD8 T-cell responses were detected against epitopes with common protease inhibitor fitness mutations. T-cell immunity to drug-resistant variants was confirmed in SHIV-infected macaques, where CD8 and CD4 immune responses to RT and protease resistance mutations were elicited using peptide-based immunotherapy.
- QRPLVTIKI carries the the L10I protease inhibition mutation and was recognized in a multidrug resistant individual. Response against wild-type epitope qrpIvtiki was detected.
- The 3 people that responded to the drug resistant forms of the virus were among those that had the highest levels of CD4 and CD8 T-cell responses, indicating that they were among the most immunocompetent.

**HXB2 Location** Protease (7–16)

**Author Location** Protease (7–16)

**Epitope** QRPLVTVKIG

**Epitope name** QG10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined epitope, QRPLVTVKIG, QG10, showed a B51-associated drug polymorphism at K14R, QRPLVTVrIG and another mutation at L10I, QRPIVTVKIG.

**HXB2 Location** Protease (11–20)

**Author Location** Pol

**Epitope** VTIKIGGQLK

**Epitope name** Pol 98

**Subtype** M

**Immunogen** vaccine, in vitro stimulation or selection, computer prediction

*Vector/Type:* DNA, peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, mouse, humanized mouse (A\*1101)

**Assay type** Cytokine production, T-cell Elispot

**Keywords** subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization

**References** McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A\*0201 and A\*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- A total of 30 variant forms of Pol 98 were identified. 50% of the variant epitopes were recognized by CTLs from mice immunized with the parental form.
- Pol 98 epitope was present in 71% of HIV sequences of many M group subtypes.

**HXB2 Location** Protease (11–20)

**Author Location** Pol (91–100)

**Epitope** VTILIGGQLK

**Immunogen** HIV-1 infection**Species (MHC)** human (A3 supertype)**Keywords** supertype, rate of progression**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** Protease (12–20)**Author Location** Pol (92–100)**Epitope** TIKIGGQLK**Immunogen** HIV-1 infection**Species (MHC)** human (A3 supertype)**Keywords** supertype, rate of progression**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** Protease (23–32)**Author Location** Pol**Epitope** LLDTGADDTV**Epitope name** L10V**Immunogen** vaccine*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3**Species (MHC)** transgenic mouse (A\*0201)**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1,

V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** Protease (23–33)**Author Location** Protease (23–33)**Epitope** LLDTGADDTV**Epitope name** LL11**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** Germany**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** immune evasion, drug resistance**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined epitope, LLDTGADDTV, LL11, has a major mutation L33F, LLDTGADDTVf associated with HLA-A2.

**HXB2 Location** Protease (29–43)**Author Location****Epitope** DDTVLEEMSLPGRWK**Immunogen** HIV-1 infection, vaccine*Vector/Type:* canarypox prime with gp120 boost, polyepitope *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease**Species (MHC)** human**Donor MHC** A\*3001, A\*3002; B\*4201/02, B\*4403/26/30**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** vaccine-induced epitopes**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.

- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Protease (30–38)

**Author Location** Pol (subtype B)

**Epitope** DTVLEEMNL

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A\*6802)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi—these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope: DTVLEDINL.
- This epitope was recognized by two different exposed and uninfected prostitutes.
- This epitope was identified by screening 49 HIV-1 peptides with the predicted A\*6802 anchor residue motif x(VT)xxxxxx(VL)

**HXB2 Location** Protease (30–38)

**Author Location** Pol (subtype A)

**Epitope** DTVLEDINL

**Subtype** A

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A\*6802)

**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 IFN $\gamma$  responses in the cervix—systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNT-VATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** Protease (30–38)

**Author Location** RT (85–93 subtype D)

**Epitope** DTVLEEWNL

**Subtype** D

**Immunogen**

**Species (MHC)** human (A\*6802)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*6802 epitope.

**HXB2 Location** Protease (30–38)

**Author Location** Pol (subtype A)

**Epitope** DTVLEDINL

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6802)

**Keywords** HIV exposed persistently seronegative (HEPS), escape

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- DTVLEDINL was recognized in 3 of the 6 women (ML857, ML1203, and ML1707), and the response was present in the last available sample prior to seroconversion, 3-7 months.
- In each of the three women, 20/20 sequences of the infecting strain had no substitutions in this epitope, all were DTVLEDINL, so there was no evidence for escape.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 3/22 HEPS sex worker controls, ML851, ML1432, and ML1601.

**HXB2 Location** Protease (30–38)

**Author Location** Pol (85–93)

**Epitope** DTVLEDINL

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A\*6802)

**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A\*6802 women, 11/12 HEPS and 6/11 HIV-1 infected women recognized this epitope likelihood ratio 4.4, p value 0.08, and HEPS women tended to respond to DTVLEDINL, infected women tended to ETAYFILKL.
- The dominant response to this HLA allele was to this epitope in 10 of the 11/12 HEPS cases, but in only 4 of the 6/11 HIV-1 infected women.

- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A\*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Four epitopes were considered to be “resistant epitopes”, as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILK(D/E)PVHGV in RT, A\*6802 DTVLEDINL in Protease, B14 DLN(M/T)LN(I/V)V in p24 and B18 FRDYV-DRF(Y/F)K also in p24.
- Subject ML 857 shifted from a A\*6802 DTVLEDINL and B35 (H/N)PDIVIIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion, and the loss of the pre-seroconversion response was not due to sequence variation within these epitopes.
- Subject ML 1203 started with CTL responses to A\*6802 DTVLEDINL and B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A\*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.
- Subject ML 1707 started with a CTL response to A\*6802 DTVLEDINL prior to seroconversion, and switched to A\*6802 ETAYFILKL and A24 RDYVDRFFKTL post-seroconversion, and the loss of the pre-seroconversion response was not due to sequence variation within the epitope.
- Subject ML 1830 made no detectable response prior to seroconversion, but responded to A\*6802 DTVLEDINL and A\*6802 ETAYFILKL post-seroconversion.

**HXB2 Location** Protease (30–38)

**Author Location** Pol

**Epitope** DTVLEDINL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6802)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2002

- Neisseria gonorrhoea cervicitis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhoea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

**HXB2 Location** Protease (30–38)

**Author Location** Pol (87–95)

**Epitope** DTVLEEMNL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A28)

**Donor MHC** A28, A29, B14, B44, Cw8

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Protease (30–38)

**Author Location** (B consensus)

**Epitope** DTVLEEMNL

**Epitope name** DL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A68)

**Donor MHC** A31, A68, B07, B70, Cw1, Cw7

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** Protease (30–38)

**Author Location**

**Epitope** DTVLEEMNL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A68)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope DTVLEEMNL elicited a magnitude of response of 565 SFC with a functional avidity of 0.5nM and binding affinity of >40,000nM.

**HXB2 Location** Protease (34–42)

**Author Location** Protease (34–42)

**Epitope** EEINLPGKW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*44)**Assay type** Other**Keywords** HLA associated polymorphism**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- EEINLPGKW was a previously defined B\*44 presented epitope that encompassed an associated polymorphism, EeINLPGKW, in the second position.

**HXB2 Location** Protease (34–42)**Author Location** Pol (2361–)**Epitope** EEMNLPGRW**Immunogen** HIV-1 infection**Species (MHC)** human (B\*4402)**Country** Australia**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape, HLA associated polymorphism**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore *et al.*, Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The fourth position of the epitope EEMnLPGRW has a mutational pattern that is correlated the host carrying HLA B\*4402.

**HXB2 Location** Protease (34–42)**Author Location** Pol (2355–)**Epitope** EEMNLPGRW**Epitope name** EW9**Immunogen** HIV-1 infection**Species (MHC)** human (B\*4403)**Country** Australia**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape, HLA associated polymorphism**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore *et al.*, Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- This HLA-B\*4403 HIV mutation association was only picked up using statistics that incorporate the phylogeny. The second position, EeMNLPGRW, is the anchor residue association.

**HXB2 Location** Protease (34–42)**Author Location** Protease (34–42)**Epitope** EEMNLPGRW**Immunogen****Species (MHC)** human (B44)**Keywords** optimal epitope**References** Frahm *et al.* 2008**HXB2 Location** Protease (34–42)**Author Location** Protease**Epitope** EEMNLPGRW**Epitope name** EW9**Immunogen** HIV-1 infection**Species (MHC)** human (B44)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** epitope processing, supervised treatment interruptions (STI), immunodominance**References** Rodriguez *et al.* 2004

- Protease and integrase are shown to be frequently targeted by CD8 T-cell responses (23% and 68% of 56 HIV+ patients, respectively). Responses tend to cluster in conserved regions of Int, although 1 high conserved region had no responses. CTL frequencies per unit protein length for Pro and Int were similar to other HIV non-structural proteins. Three novel HLA class I-restricted optimal epitopes were found and characterized with fine mapping.
- The epitope includes residue M36, which is a known accessory mutation site in individuals treated with PIs.

**HXB2 Location** Protease (34–42)**Author Location** Protease (34–42)**Epitope** EEMNLPGRW**Epitope name** EW9**Subtype** multiple**Immunogen** HIV-1 infection**Species (MHC)** human (B18, B40, B44)**Country** Germany**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** immune evasion, drug resistance**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This highly immunogenic index epitope, EEMNLPGRW, EW9, developed variants EEiNLPGRW, EW9 M/I, EEMdLPGRW, EW9 N/D, EdMNLPGRW, EW9 E/D, EdiNLPGRW, EW9 D/I, EEMNLPgkW, EW9 R/K, EEMNLsGRW, EW9 P/S. E35D and P39S mutants were located in the previously reported HLA-B44 restricted epitope EEMSLPGRW (EW9). Correlation between minor drug mutation E35D and B44 was strong, standing up to Bonferroni's correction, while that of B44 with P39S was weak. E35D mutations induced a strong decrease in CTL recognition, but few patient samples did mount specific responses against it giving a negative correlation between this mutation and HLA-B44. A novel association between the E35D mutant and HLA-B18 was also found.
- Cross-reactivity of CTL recognition of EW9 and variants occurred for most patients. This showed that cells from several patients mount oligoclonal CTL responses, indicating immune system reactions to escape by recruitment of CTLs with new TCR specificities. On the other hand, most patients showed mutually exclusive recognition of variant epitopes containing either E35D or E35E; HLA-B44 subtypes and other factors tested could not explain this phenomenon.
- EW9 epitope and variant peptides include the S37N substitution when compared to HXB2 strain sequences.

**HXB2 Location** Protease (38–47)

**Author Location** Protease (38–47)

**Epitope** LPGRWKPKMI

**Epitope name** LI10

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw3)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations

(positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.

- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined Cw3-associated epitope LPGRWKPKMI, LI10, shows minor mutations at K43.

**HXB2 Location** Protease (42–50)

**Author Location** Protease (42–50)

**Epitope** WKPKMIGGI

**Epitope name** WI9

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw3)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined Cw3-associated epitope WKPKMIGGI, WI9, shows minor mutations at K43.

**HXB2 Location** Protease (45–53)

**Author Location** Protease (45–53)

**Epitope** KMIGGIGGF

**Epitope name** KF9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined epitope, KMIGGIGGF, KF9, was the optimal HLA-B62 restricted epitope.

**HXB2 Location** Protease (45–54)

**Author Location** Protease (45–54)

**Epitope** KMIGGIGGFI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

**HXB2 Location** Protease (45–54)

**Author Location** Pol (45–54 IIIB)

**Epitope** KMIGGIGGFI

**Epitope name** pol45-54

**Subtype** B

**Immunogen** vaccine

**Vector/Type:** DNA **Strain:** B clade IIIB

**HIV component:** Gag-Pol

**Species (MHC)** humanized mouse (A\*0201)

**Assay type** Intracellular cytokine staining

**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance, variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Singh & Barry 2004

- When A\*0201-C3H/J transgenic mice were immunized with plasmids encoding wild-type gag-pol, codon-optimized (CO) gag-pol, and an expression library vaccine expressing 16 fragments of gag-pol fused with ubiquitin for proteasome targeting (ELI), the ELI vaccine produced up to 10-fold higher CD8 T-cell responses than the other two vaccines. In contrast to the wt and CO vaccines, which tended to augment only immunodominant responses, boosting with the ELI vaccine resulted in many CD8 responses against variant epitopes from different HIV-1 clades, and against drug-resistant variants.
- The drug resistant variant of this epitope, kViVgiggi, was tested. WT and CO vaccines produced low level CD8+ T-cell responses against the B clade form as well as against drug resistant variant, but the ELI vaccine produced much more intense responses against both the WT and the variant, including after boosting.

**HXB2 Location** Protease (45–54)

**Author Location** Pol (125–134)

**Epitope** KMIGGIGGFI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

**HXB2 Location** Protease (45–54)

**Author Location** Protease (45–54)

**Epitope** KMIGGIGGFI

**Epitope name** KI10

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2, B62)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This previously known index epitope, KMIGGIGGFI, KI10, developed major mutations KiIGGIGGFI, KI10-I/L and variant KMIGGIGGFv, KI10-V. In most patients, CTL responses were generated against both index and variant epitopes, suggesting that different CTL clones within each patient show different recognition specificities. However, one patient was unable to recognize both M46I and I54V mutations, while others responded to mutants and not the index epitope. Other drug resistance-associated mutations for this epitope are I47A/V/L, G48V/M, I50L/V, F53L and I54A/L/M. HLA-A2 showed greater correlations than HLA-B62 did for this epitope.

**HXB2 Location** Protease (55–63)

**Author Location** Protease (55–63)

**Epitope** KVRQYDQIL

**Epitope name** KL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2, Cw6)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.

- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined epitope, KVRQYDQIL, KL9, spawns a minor A2-associated minor mutation at I62V, KVRQYDQvL and an identical Cw6-associated drug polymorphism at the same position.

**HXB2 Location** Protease (56–66)

**Author Location** Protease (56–66)

**Epitope** VRQYDQIPIEI

**Epitope name** VI11

**Immunogen** HIV-1 infection

**Species (MHC)** human (B13)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined epitope, VRQYDQIPIEI, VI11, shows drug-induced mutations I62V, VRQYDQvPIEI and E65D, VRQYDQIPIIdI.
- VI11 epitope and variant peptides include the L63P substitution when compared to HXB2 strain sequences.

**HXB2 Location** Protease (57–66)

**Author Location** Pol (113–122)

**Epitope** RQYDQILIEI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*13)

**Donor MHC** A\*0301, A\*3001, B\*1301, B\*1402, Cw\*0602, Cw\*0802

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining



**Keywords** epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism

**References** Honeyborne *et al.* 2007

- To determine whether HLA-B\*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B\*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B\*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.

**HXB2 Location** Protease (57–66)

**Author Location**

**Epitope** RQYDQILIEI

**Epitope name** RI10

**Immunogen**

**Species (MHC)** human (B13)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B13 epitope. Variant RQYDQIPiEI also noted.

**HXB2 Location** Protease (57–66)

**Author Location** Protease (57–66)

**Epitope** RQYDQIPiEI

**Epitope name** RI10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B13)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined B13-associated epitope, RQYDQIPiEI, RI10, shows drug-induced mutations at I62V, RQYDQvPIEI. RI10 does not have a published HLA-binding motif yet, but it overlaps with the Cw4-restricted epitope QYDQIPiEI, and

shows similarity at the putative anchor binding positions of the B13-restricted Nef epitope, RQDILDWLWI.

**HXB2 Location** Protease (58–66)

**Author Location** Protease

**Epitope** QYDQIPiEI

**Epitope name** QI9

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0401)

**Donor MHC** A\*0201, A\*1101, B\*1501, B\*3501, Cw\*0401, Cw\*0701

**Country** Australia

**Assay type** Intracellular cytokine staining

**Keywords** HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization, optimal epitope

**References** Stratov *et al.* 2005

- CD8 T-cells targeting epitopes spanning drug resistance induced mutations were detected in 3/25 individuals harboring multidrug-resistant HIV-1. Novel CD8 T-cell responses were detected against epitopes with common protease inhibitor fitness mutations. T-cell immunity to drug-resistant variants was confirmed in SHIV-infected macaques, where CD8 and CD4 immune responses to RT and protease resistance mutations were elicited using peptide-based immunotherapy.
- QYDQIPiEIW harbors the L63P protease inhibitor mutation, and this created an epitope. The wild-type epitope qydqILieI was not recognized.
- The 3 people that responded to the drug resistant forms of the virus were among those that had the highest levels of CD4 and CD8 T-cell responses, indicating that they were among the most immunocompetent.

**HXB2 Location** Protease (62–70)

**Author Location** Protease (62–70)

**Epitope** ILIEICGHK

**Epitope name** IK9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.

- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined epitope, ILIEICGHK, IK9, has a variant K70R, ILIEICGHr which strongly reduced recognition by CTL as it is a C-terminal anchor site. Also the minor mutation I64V, ILvEICGHK, is negatively associated with HLA-A3, indicating that it rarely occurs in A3-patients.

**HXB2 Location** Protease (64–73)

**Author Location** Protease (64–73)

**Epitope** IEICGHKAIG

**Epitope name** IG10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B18, B40, B44)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations (positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.
- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined epitope, IEICGHKAIG, IG10, spawned B44- and B18-associated minor mutations as A71V/T - IEICGHKvIG, IEICGHKtIG and a B18-associated polymorphism at K70 - IEICHHKAIG. IG10 was also recognized by B40-positive patients whose HLA belongs to the B44 super-type.

**HXB2 Location** Protease (68–76)

**Author Location** (C consensus)

**Epitope** GKKAIGTVL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- GKKAIGTVL is an optimal epitope.

**HXB2 Location** Protease (68–76)

**Author Location**

**Epitope** GKKAIGTVL

**Epitope name** GL9

**Immunogen**

**Species (MHC)** human (B\*1503)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1503 epitope.

**HXB2 Location** Protease (69–83)

**Author Location** Protease (69–83)

**Epitope** HKAIGTVLVGPTPVN

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** TCR usage, characterizing CD8+ T cells

**References** Yang *et al.* 2005a

- CTL responses were evaluated in identical twins infected with HIV-1 from the same blood source. Targeting of the CTL was similar in the 2 patients, while their TCR profiles were highly dissimilar. It is suggested that CTL targeting is predominately genetically determined, while T-cell generation is a stochastic process; the responding CTLs differ at the TCR molecular level, leaving the viral escape and CTL efficacy unpredictable.
- HKAIGTVLVGPTPVN was the immunodominant epitope in each twin, but was recognized by T cells with distinctly different TCRs. The epitope was not defined within the epitope. The twins had very different patterns of HIV evolution in this region, with one carrying HKveGsVLiGPTPVN and the other HKAIGaVLiGPTPVN.

**HXB2 Location** Protease (70–77)

**Author Location**

**Epitope** KAIGTVLV

**Immunogen**

**Species (MHC)** human (B57)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B57 epitope.

**HXB2 Location** Protease (70–77)

**Author Location** Protease

**Epitope** KAIGTVLV

**Epitope name** KV8

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B58, B63)

**Donor MHC** A23, A30, B42, B57, Cw17

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- HLA-B63/57/58 epitope containing the B58 supertype binding motif. Significantly more often recognized by B63-positive subjects than by negative subjects. Optimal epitope was defined in a person who was B57+.

**HXB2 Location** Protease (75–84)**Author Location** Protease (75–84 MN)**Epitope** VLVGPTPVNI**Immunogen** in vitro stimulation or selection**Species (MHC)** human (A\*0201)**Keywords** binding affinity**References** Konya *et al.* 1997

- Peptide predicted to be reactive based on HLA-A\*0201 binding motif.
- Peptide could stimulate CTL in PBMC from 5/6 seronegative donors.
- Peptide located in a highly conserved region of protease.
- Both 9-mer and 10-mer could stimulate CTL: VLVGPTPVNI and LVGPTPVNI.
- Binding affinity to A\*0201 was measured,  $C_{1/2 \max} \mu\text{M} = 6$  for 10-mer, 3 for 9-mer.
- MAL variant of Pr(75-84 MN), with substitutions V77, G78, and P79, gave reduced binding and CTL recognition.

**HXB2 Location** Protease (75–84)**Author Location** Protease (175–184 MN)**Epitope** VLVGPTPVNI**Subtype** B**Immunogen** vaccine*Vector/Type:* DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)**Species (MHC)** humanized mouse (A\*0201)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy**References** Isagulians *et al.* 2004

- Immunization of HLA-A\*0201-transgenic mice with synthetic genes encoding clusters of human A\*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains.
- This was one of five HLA-A\*0201 epitopes from the RT or protease proteins that was included in the polyepitope vaccine. When the transgenic HLA A\*0202 mice were vaccinated with the polyepitope construct or with a mixture of RT peptides, a sustained low level CD8+ T-cell gamma IFN response was

observed, in contrast to when an intact RT gene was used for vaccination.

**HXB2 Location** Protease (75–84)**Author Location** Pol (75–84 IIIB)**Epitope** VLVGPTPVNI**Epitope name** pol75-84**Subtype** B**Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade IIIB  
*HIV component:* Gag-Pol**Species (MHC)** humanized mouse (A\*0201)**Assay type** Intracellular cytokine staining**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance, variant cross-recognition or cross-neutralization, vaccine antigen design**References** Singh & Barry 2004

- When A\*0201-C3H/J transgenic mice were immunized with plasmids encoding wild-type gag-pol, codon-optimized (CO) gag-pol, and an expression library vaccine expressing 16 fragments of gag-pol fused with ubiquitin for proteasome targeting (ELI), the ELI vaccine produced up to 10-fold higher CD8 T-cell responses than the other two vaccines. In contrast to the wt and CO vaccines, which tended to augment only immunodominant responses, boosting with the ELI vaccine resulted in many CD8 responses against variant epitopes from different HIV-1 clades, and against drug-resistant variants.
- The drug resistant variant of this epitope, vlvgptpTnV, was tested. WT and CO vaccines produced low level CD8+ T-cell responses against the B clade form as well as against drug resistant variant, but the ELI vaccine produced much more intense responses against both the WT and the variant, including after boosting.

**HXB2 Location** Protease (75–84)**Author Location** Protease (75–84)**Epitope** VLVGPTPVNI**Immunogen** vaccine*Vector/Type:* peptide, Other *Strain:* multiple epitope immunogen *HIV component:* Protease *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Other**Species (MHC)** transgenic mouse (A\*0201)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** vaccine-specific epitope characteristics, drug resistance**References** Boberg *et al.* 2006

- Binding of a protease epitope and its variants caused by drug-resistance mutations to HLA-A0201 and CTL responses in transgenic mice immunized with this epitope were analyzed. It was found that both the wild-type and resistance variants of the epitope bound well to HLA-A0201 and were strongly immunogenic in HLA-A0201 transgenic mice. Immunological cross-reactivity between different variants of the peptide was observed, suggesting that immunization with drug-resistance mutated epitopes could induce a broad immune response, which may cause a better outcome of antiretroviral therapy in HIV-1 infected individuals.

- An interesting epitope from the HIV-1 protease (PR) protein was found VLVGPTPVNI, and mutant variants - VLVGPT-PaNI, VLVGPTPfNI, VLVGPTPVNv, VLVGPTPfNv. The epitope, VLVGPTPVNI, and its drug-induced mutant version VLVGPTPfNv, were studied and were able to elicit responses both by peptide constructs and multi-CTL epitope constructs.

**HXB2 Location** Protease (76–84)

**Author Location** Protease (76–84)

**Epitope** LVGPTPVNI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naïve subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

**HXB2 Location** Protease (76–84)

**Author Location** Pol (163–)

**Epitope** LVGPTPVNI

**Epitope name** Pol-163

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity, subtype comparisons, super-type, computational epitope prediction

**References** Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- LVGPTPVNI binds to 4/5 HLA-A2 supertype alleles: A\*0201, A\*0202, A\*0206 (highest affinity) and A\*6802, but not A\*0203.
- 1/22 individuals with chronic HIV-1 infection recognized this epitope by ELISPOT.

- 0/12 acutely infected individuals recognized this epitope.

**HXB2 Location** Protease (76–84)

**Author Location** Protease (76–84)

**Epitope** LVGPTPVNI

**Epitope name** LI9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a A\*0201 epitope.

**HXB2 Location** Protease (76–84)

**Author Location** Protease (76–84)

**Epitope** LVGPTPVNI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naïve individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naïve T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, LVGPTPVNI, was predicted to be restricted by HLA A\*0201, A\*0202, A\*0205, A\*0209, B\*1501 and B\*1516.

**HXB2 Location** Protease (76–84)

**Author Location** Protease

**Epitope** LVGPTPANI

**Immunogen** HIV-1 infection

**Species (MHC)** human, macaque (A\*0205)

**Donor MHC** A\*0101, A\*0205, B\*0702, B\*0801, Cw\*0701, Cw\*0702

**Country** Australia

**Assay type** Intracellular cytokine staining

**Keywords** HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization

**References** Stratov *et al.* 2005

- CD8 T-cells targeting epitopes spanning drug resistance induced mutations were detected in 3/25 individuals harboring multidrug-resistant HIV-1. Novel CD8 T-cell responses were detected against epitopes with common protease inhibitor fitness mutations. T-cell immunity to drug-resistant variants was confirmed in SHIV-infected macaques, where CD8 and CD4

immune responses to RT and protease resistance mutations were elicited using peptide-based immunotherapy.

- A response against the peptide harboring the protease drug resistance mutation V82A, LVGPTPANI, was detected in one individual, but the wildtype epitope was not recognized, lvgptpVni. This epitope response was not fine-mapped, and is based on analogy to a previously described A2 epitope.
- Other drug resistant variants were not recognized: V82T and I84V.
- The 3 people that responded to the drug resistant forms of the virus were among those that had the highest levels of CD4 and CD8 T-cell responses, indicating that they were among the most immunocompetent.

**HXB2 Location** Protease (76–84)

**Author Location**

**Epitope** LVGPTPVNI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A02)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope LVGPTPVNI elicited a magnitude of response of 480 SFC with a functional avidity of 0.005nM and binding affinity of 10.1nM.

**HXB2 Location** Protease (76–84)

**Author Location** Protease (76–84 HXB2)

**Epitope** LVGPTPVNI

**Epitope name** PR82V

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** Intracellular cytokine staining, Chromium-release assay

**Keywords** HAART, ART, escape

**References** Karlsson *et al.* 2003

- This epitope contains two positions that are commonly associated with protease inhibitor escape, lvgptpAni (V82A) and lvgptpvnV (I84V). 29 HIV-1 infected patients (15 were HLA-A2+) with a history of protease inhibitor failure were screened for mutations within the protease gene and CD8+ T cells recognition of the wt and V82A variant peptides. CTL pressure alone, despite high functional avidity, did not drive the V82A substitution. Surprisingly V82A was found more frequently among HLA-A2- individuals (10/14) than HLA-A2+ (7/15), despite the mutation conferring not only drug resistance but CTL escape.

- 8/15 HLA-A2+ patients carried had a Val at position 82; 7/8 of these recognized the WT peptide, but only 3/8 could also recognize V82A.

- 7/15 had the V82A substitution; 2/7 recognized the wt and the V82A mutation, 1/7 recognized only the peptide with the V82A substitution.

**HXB2 Location** Protease (76–84)

**Author Location** Protease (76–84)

**Epitope** LVGPTPVNI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Canada

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** HAART, ART, escape, immunotherapy, variant cross-recognition or cross-neutralization

**References** Mason *et al.* 2004

- Accumulation of specific antiretroviral drug-resistance mutations in Pol gene was shown to sustain and even enhance the antigenicity and immunogenicity of HIV-1 CTL epitopes in this region. Several different patterns of cross-reactivity and selective recognition of wild-type and variant epitopes were found.
- LVGPTPVNI variant is detected due to appearance of I84V resistance mutation. Three patients receiving PIs had viral sequences obtained, and two had the I84V mutation. Elispot reactivity to this epitope in either form was evident in these patients, showing drug resistance can persist coincident with an active CTL response.

**HXB2 Location** Protease (76–84)

**Author Location** Protease (76–84)

**Epitope** LVGPTPVNI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** acute/early infection, optimal epitope

**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection.

**HXB2 Location** Protease (76–84)

**Author Location** Protease (76–84)

**Epitope** LVGPTPVNI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Canada

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** variant cross-recognition or cross-neutralization, characterizing CD8+ T cells, mimics

**References** Mason *et al.* 2005

- CTL responses against the human IP-30 signal peptide sequence LLDVPTAAV were shown to be elicited by stimulation of PBMCs from HIV-1 infected individuals with HIV protease peptide 76-84, LVGPTPVNI. In vitro stimulation with HIV PR 76-84 or the IP-30 signal peptide was shown to activate a comparable population of cross-reactive effector cells. None of the peptides activated CTL in non-HIV-infected individuals. IP-30 signal peptide was shown to have lower avidity T-cell interactions than the HIV peptide.
- As a control, responses to A2-restricted HIV epitopes ALVEICTEM, EELRQHLLRW, and LSPRTLNAW were shown not to give IP-30 responses.

**HXB2 Location** Protease (76–84)

**Author Location** Protease

**Epitope** LVGPTPVNI

**Epitope name** A2-LI9(Pro)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Protease (76–84)

**Author Location** Pol (156–164)

**Epitope** LVGPTPVNI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 superotypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

**HXB2 Location** Protease (76–85)

**Author Location** (C consensus)

**Epitope** LVGPTPVNII

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- LVGPTPVNII is an optimal epitope.

**HXB2 Location** Protease (77–85)

**Author Location** Pol

**Epitope** VGPTPVNII

**Epitope name** V

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism

**References** Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
- Clade-B vaccination induced recognition of index epitope VGPTPVNII and variant VGPTPiNII.

**HXB2 Location** Protease (77–85)

**Author Location** Protease (C-96BW15C05)

**Epitope** IGPTPVNII

**Epitope name** D

**Subtype** C

**Immunogen** vaccine

*Vector/Type:* DNA, alphavirus replicon *Strain:* C clade C-96BW04.09, C clade C-96BW15C05 *HIV component:* Gag, Gag-Pol, Pol

**Species (MHC)** mouse (H-2d)

**Assay type** Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, vaccine antigen design

**References** Megede *et al.* 2006

- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
- This is a novel epitope.

**HXB2 Location** Protease (79–89)

**Author Location** Protease

**Epitope** PTPVNIIGRNL

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B63)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- Putative HLA-B63/57/58 epitope containing the B58 super-type binding motif. Significantly more often recognized by B63-positive subjects than by negative subjects, trend towards being more often recognized in those with B57/B58.

**HXB2 Location** Protease (80–90)

**Author Location** (C consensus)

**Epitope** TPVNIIGRNMML

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- TPVNIIGRNMML is an optimal epitope.

**HXB2 Location** Protease (80–90)

**Author Location** Protease (80–90)

**Epitope** TPVNIIGRNMML

**Epitope name** TL11

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other

**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism

**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction

**HXB2 Location** Protease (80–90)

**Author Location** Protease (80–90)

**Epitope** TPVNIIGRNMML

**Epitope name** TL11

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** optimal epitope

**References** Honeyborne *et al.* 2006

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B\*3910, B\*4201, B\*8101 and Cw\*1801, by motif inference. HLA-A\*2902 was found to overlap those of A1 and A24 superotypes.
- TPVNIIGRNMML (TL11) was the optimal epitope for HLA-B\*8101 with variants TPVNIIGRNM, PVNIIGRNMML, TPVNIIGRNMMLt, pTPVNIIGRNMML having been tested.

**HXB2 Location** Protease (80–90)

**Author Location**

**Epitope** TPVNIIGRNMML

**Epitope name** TL11

**Immunogen**

**Species (MHC)** human (B81)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B81 epitope.

**HXB2 Location** Protease (91–99)

**Author Location** Pol (2529–)

**Epitope** TQIGCTLNF

**Epitope name** B\*1501 TF9

**Subtype** B, C, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1501)

**Country** Australia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, HLA associated polymorphism

**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore et al., Science 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- The mutational pattern in the third position in this epitope TQIGCTLNF, is correlated with the host carrying HLA B\*1501.
- This epitope was experimentally tested using Interferon-g Elispot and functional avidity studies. For one of six patients tested, the form TQ(L)GCTLNF showed decreased functional avidity relative to TQIGCTLNF. In all other patients, the form TQ(L)GCTLNF had greater functional avidity than the form TQIGCTLNF.

**HXB2 Location** Protease (91–99)

**Author Location** Protease

**Epitope** TQIGCTLNF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, rate of progression, immunodominance

**References** Frahm *et al.* 2006

- CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects in spite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- TQIGCTLNF of clade B is a potential HLA-B\*1503-restricted epitope, with epitope TQIGCTLNF found in clade C.

**HXB2 Location** Protease (91–99)

**Author Location** Protease (91–99)

**Epitope** TQICGTLNF

**Epitope name** TF9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62, Cw3)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** immune evasion, drug resistance

**References** Mueller *et al.* 2007

- To assess HIV-1-specific CTL influence on development and patterns of drug resistance in protease (PR) 94 HLA-typed patients were analyzed. Statistical analyses performed were univariate (Fisher's exact test) and were verified with biological assays. 10 new CTL epitopes were defined and 26 correlations

(positive and negative) between HLA class-I alleles and PR mutations - some leading to escape mutations - were detected, demonstrating that CTL epitopes can be predicted based on HLA-amino acid substitution associations.

- Some patient CTL escape mutations were detectable by other CTLs of the same patient. Correlations between resistance mutations, polymorphisms and specific PR inhibitors were not detected.
- HLA-B had the strongest impact on PR sequence change, though HLAs-A and -C also had some impact.
- The authors suggest that CTL escape is active in developing drug-resistance related polymorphisms as well as major and minor mutations in HIV-1 infected persons.
- HIV-1 subtype breakdown in this cohort was follows - 83/94 patients infected with subtype B virus, 3 with subtype C, 4 CRF01\_AE, 1 CRF03\_AB, 1 CRF15\_01B and 2 subtype Ds.
- This newly defined epitope, TQICGTLNF, TF9, spawns minor B62 and Cw3-associated mutations at I93L, viz. TQICGTLNF.

## II-B-11 Protease-RT CTL/CD8+ epitopes

**HXB2 Location** Protease-RT (95–5)

**Author Location** Gag (175–184)

**Epitope** CTLNFPISPI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- The epitope starts in Protease and ends in RT.
- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802)

**HXB2 Location** Protease-RT (96–5)

**Author Location** Pol (176–184)

**Epitope** TLNFPISPI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.



- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNP to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

- HXB2 Location** Protease-RT (96–5)  
**Author Location** Pol (152–160)  
**Epitope** TLNFPISPI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding  
**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism  
**References** Reche *et al.* 2006
- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
  - A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
  - This epitope, TLNFPISPI, was predicted to be restricted by HLA A\*0201 and A\*0207.

## II-B-12 RT CTL/CD8+ epitopes

- HXB2 Location** RT (1–16)  
**Author Location** (C consensus)  
**Epitope** PISPIETVPVCLKPGM  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3910)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- HXB2 Location** RT (3–12)  
**Author Location** RT (3–12)  
**Epitope** SPIETVPVKL  
**Subtype** B  
**Immunogen** HIV-1 infection

- Species (MHC)** human (A\*02)  
**Country** United States  
**Assay type** Intracellular cytokine staining, Other  
**Keywords** rate of progression, escape, immune evasion  
**References** Karlsson *et al.* 2007
- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

- HXB2 Location** RT (3–12)  
**Author Location** RT (LAI)  
**Epitope** SPIETVPVKL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2, B61)  
**References** van der Burg *et al.* 1997
- Recognized by CTL from a long-term survivor, EILKEPVGHGCV was also recognized.
  - Highly conserved across clades.

- HXB2 Location** RT (3–12)  
**Author Location** (C consensus)  
**Epitope** SPIETVPVKL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*8101)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - Mutational patterns in the P2 residue of SPIETVPVKL are associated with the presence of the HLA presenting molecule in the host.

- HXB2 Location** RT (3–12)  
**Author Location** RT (3–12)  
**Epitope** SPIETVPVKL  
**Epitope name** SL10  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other

**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism

**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction

**HXB2 Location** RT (3–12)

**Author Location** Pol

**Epitope** SPIETVPVKL

**Epitope name** SL10

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** rate of progression, HLA associated polymorphism

**References** Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than "other" HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by "other", non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also showed lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variants SsIETVPVKL and SPIkTVPVKL at positions 2 and 4 were the predominant polymorphisms found.

**HXB2 Location** RT (3–12)

**Author Location** Pol

**Epitope** SPIETVPVKL

**Immunogen**

**Species (MHC)** human (B7)

**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.

- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFN $\gamma$  production in an ELISPOT assay.

- SPIETVPVKL was newly identified as HLA-B7 epitope in this study, it had been previously shown to be presented by HLA-A2 and B61.

**HXB2 Location** RT (3–12)

**Author Location** Pol

**Epitope** SPIETVPVKL

**Epitope name** 1307

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2, B61, B7, B8)

**Donor MHC** A03, A24, B07, B38, Cw07, Cw12/13; A29, A30, B08, B44, Cw07, Cw16

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC superotypes.
- Estimated binding probability for SPIETVPVKL: 12%. Promiscuous epitope binding to A02, B07, B08 and B61.

**HXB2 Location** RT (5–12)

**Author Location** RT (5–12)

**Epitope** IETVPVKL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4001)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** RT (5–12)

**Author Location** Pol (160–167)

**Epitope** IETVPVKL

**Epitope name** IL8

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4001)

**Donor MHC** A\*0201, A\*2402, B\*4001, B\*5001, Cw03, Cw04

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization

**References** Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, IETVPVKL (IL8), restricted by HLA-B\*4001, had variants IdTVPVKL and IETVPVrL arise.

**HXB2 Location** RT (5–12)

**Author Location** Pol

**Epitope** IETVPVKL

**Epitope name** IL-8

**Immunogen** HIV-1 infection

**Species (MHC)** human (B40)

**Assay type** Other

**Keywords** escape, TCR usage, immune evasion

**References** Yu *et al.* 2007b

- The dependence of TCR clonotype recruitment on genetic background was determined by studying monozygotic twins infected with the same HIV-1 strain. After an early, initial correlation in the magnitude, specificity and immunodominance of CTL response [Draenert *et al.* J. Exp. Med. 203:529-539(2006)], subsequent disease was mixed with respect to CTL epitopes' mutational escape. TCR alpha and beta chain repertoires were analyzed and it was found that their clonotypes in HIV-specific CTLs were broadly heterogeneous for both concordant and discordant epitope sequence evolution between the twins. Therefore initial TCR recruitment appears to be an entirely random process independent of genetic background of the infected individual.
- This epitope, IL8, showed discordant epitope evolution between the twins, and both alpha and beta TCR chains recruited were entirely different between them.

**HXB2 Location** RT (5–29)

**Author Location** RT (160–184 HXB2)

**Epitope** IETVPVKLPGMDGPKVKQWPLTEE

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Walker *et al.* 1989

- One of five epitopes defined for RT-specific CTL clones in this study.

**HXB2 Location** RT (14–23)

**Author Location** Pol

**Epitope** PGMDGPKVKQ

**Epitope name** 1276

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A68, B42, B45, Cw16, Cw17

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for PGMDGPKVKQ:52% Promiscuous epitope binding to A11 or A68, previously published B8.

**HXB2 Location** RT (15–32)

**Author Location** (C consensus)

**Epitope** GMDGPKVKQWPLTEEEKIK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4202)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (18–26)

**Author Location** RT (185–193 LAI)

**Epitope** GPKVKQWPL

**Subtype** B

**Immunogen**

**Species (MHC)** human (B\*0801)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0801 epitope.

**HXB2 Location** RT (18–26)

**Author Location** RT (18–26)

**Epitope** GPKVKQWPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.

- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, GPKVKQWPL, was predicted to be restricted by HLA B\*0702, B\*0801, B\*3501, B8.

**HXB2 Location** RT (18–26)  
**Author Location** RT (18–26)  
**Epitope** GPKVKQWPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Meier *et al.* 1995; Menendez-Arias *et al.* 1998

- HIV proteins with mutations in this epitope allowed transactive inhibition of specific CTL-mediated lysis.
- Article reviewed in Menendez-Arias *et al.* [1998], with a discussion of antagonism.

**HXB2 Location** RT (18–26)  
**Author Location** RT (173–181)  
**Epitope** GPKVKQWPL  
**Immunogen**  
**Species (MHC)** human (B8)  
**References** Goulder *et al.* 1997g; Menendez-Arias *et al.* 1998

- Included in a study of the B8 binding motif.
- Article reviewed in Menendez-Arias *et al.* [1998], with a discussion of antagonism.

**HXB2 Location** RT (18–26)  
**Author Location** RT (185–193 LAI)  
**Epitope** GPKVKQWPL  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (B8)  
**References** Sutton *et al.* 1993

- Predicted epitope based on B8-binding motifs, from larger peptide IETVPVKLKPMDGPKVKQWPLTEE.

**HXB2 Location** RT (18–26)  
**Author Location** RT (185–193 LAI)  
**Epitope** GPKVKQWPL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Klenerman *et al.* 1995; Menendez-Arias *et al.* 1998

- Naturally occurring antagonist GPRVKQWPL found in viral PBMC DNA and RNA.
- Article reviewed in Menendez-Arias *et al.* [1998] with a discussion of antagonism.

**HXB2 Location** RT (18–26)  
**Author Location** RT (18–26)  
**Epitope** GPKVKQWPL  
**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (B8)  
**Keywords** dendritic cells  
**References** Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYK-TLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

**HXB2 Location** RT (18–26)  
**Author Location** RT (185–193)  
**Epitope** GPKVKQWPL  
**Epitope name** GPK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, escape, acute/early infection  
**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- Two of the 7/8 study subjects that were HLA B8+ recognized this epitope.
- Patient SC2 (HLA A1, B7/8, Cw0701/0702, DR4/53, DQ7) had CTL responsiveness against epitopes FLKEKGGL, GPKVKQWPL, and GEIYKRWII peptides – FLKEKGGL tetramer staining steadily declined and at day 1340 the FLKEKGGL stained cells were no longer detected and the escape mutant FLKENGGI was found in 8/10 clones.
- Patient SC11 (HLA A1, B8, Cw0201, DR3/11, DR52, DQ2/7) started therapy early, remained on therapy for 40 days, then reinitiated HAART at day 640 had a CTL response to FLKEKGGL, GPKVKQWPL, and GEIYKRWII throughout and received a benefit from the early limited course therapy.

**HXB2 Location** RT (18–26)  
**Author Location** Pol  
**Epitope** GPKVKQWPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** HAART, ART  
**References** Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.

**HXB2 Location** RT (18–26)

**Author Location** RT (185–193 SF2)

**Epitope** GPKVKQWPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/3 group 2, and 2/2 group 3.

**HXB2 Location** RT (18–26)

**Author Location** Pol (171–180)

**Epitope** GPKVKQWPL

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B8)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- GPKVKQWPL is cross-reactive for clades A, B, C, and D.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** RT (18–26)

**Author Location** RT (18–26)

**Epitope** GPKVKQWPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

**HXB2 Location** RT (18–26)

**Author Location** RT

**Epitope** GPKVKQWPL

**Epitope name** GPK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** RT (18–26)

**Author Location** Pol (171–180)

**Epitope** GPKVKQWPL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** Th1, characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN- $\gamma$  and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN- $\gamma$  only, and the other one (Tc1c) secretes GzB only.
- One of the patients responded to this peptide with GzB producing cells, while two different patients responded with IFN- $\gamma$  producing cells.

**HXB2 Location** RT (18–26)

**Author Location** (B consensus)

**Epitope** GPKVKQWPL

**Epitope name** GL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A25, A32, B08, B14, Cw7, Cw8

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN- $\gamma$  and TNF- $\alpha$  exhibit stronger cytotoxic activity than those secreting only IFN- $\gamma$ . These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** RT (18–26)

**Author Location** Pol (173–181)

**Epitope** GPKVKQWPL  
**Epitope name** GL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Donor MHC** A\*01, A\*11, B\*08, B\*15, Cw\*04, Cw\*07  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** escape, variant cross-recognition or cross-neutralization, optimal epitope  
**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The GL9 variant GPrVKQWPL was essentially the only form of the epitope detected over a 5-year period in this person. Elispot reactions were roughly equivalent between the autologous form and the B clade consensus form, GPKVKQWPL. A single variant was observed in 1/8 clones at the 5-year time point, GPrVKQgPL.

**HXB2 Location** RT (18–26)  
**Author Location** RT  
**Epitope** GPKVKQWPL  
**Epitope name** B8-GL9(RT)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (18–26)  
**Author Location**  
**Epitope** GPKVKQWPL  
**Immunogen**  
**Species (MHC)** (B8)

**Keywords** review, immunodominance, escape, vaccine antigen design

**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

**HXB2 Location** RT (18–27)

**Author Location** Pol

**Epitope** GPKVKQWPLT

**Immunogen**

**Species (MHC)** human (B7, B8)

**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFN $\gamma$  production in an ELISPOT assay.
- GPKVKQWPLT was confirmed as a previously identified HLA-B8 epitope, and newly identified as an HLA-B7 epitope in this study.

**HXB2 Location** RT (18–27)

**Author Location** Pol

**Epitope** GPKVKQWPLT

**Epitope name** 1293

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7, B8)

**Donor MHC** A03, A24, B07, B38, Cw07, Cw12/13; A29, A30, B08, B44, Cw07, Cw16

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for GPKVKQWPLT: 27% Promiscuous epitope binding to B07 and B08.

**HXB2 Location** RT (33–41)

**Author Location** RT (33–41)

**Epitope** ALVEICTEM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Donor MHC** A\*01, B\*08

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- In one patient, initially the consensus sequence ALVEICTEM was not found. Instead the 35I variant ALiEICTEM was seen, followed by the emergence of the 35M variant, ALmEICTEM, and finally, emergence of the consensus B sequence, ALvEICTEM. Strongest immune responses were detected to the 35M variant and weaker responses to the 35I variant, while negligible responses were seen to the consensus, ALVEICTEM. This is an example of CTL-responses against variant epitopes causing virus evolution to the consensus B sequence. Other variants that emerged were ALtEICTEM, ALiEICTEt, ALiEICTdM, ALmkICTEM and ALmEiCaEM.
- Responses to epitope ALVEICTEM were seen in early chronic infection. This was one of the epitopes targeted by broad HLA-A2-restricted CTL responses.

**HXB2 Location** RT (33–41)**Author Location** RT (33–41 LAI)**Epitope** ALVEICTEM**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0201 epitope.

**HXB2 Location** RT (33–41)**Author Location** RT (33–41 LAI)**Epitope** ALVEICTEL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201)**Keywords** binding affinity, computational epitope prediction**References** Samri *et al.* 2000

- This epitope contains the mutation M41L, a mutation induced by nucleoside reverse transcriptase inhibitors.
- Patient 201#5, (A\*0201), was found by ELISPOT to recognize the mutated peptide after zidovudine treatment, but not the wild-type peptide – the mutation M41L gave an increased A2 binding score ([http://bimas.dcrn.nih.gov/molbio/hla\\_bind](http://bimas.dcrn.nih.gov/molbio/hla_bind)) compared to the wildtype RT sequence.

- Three additional A\*0201 individuals and one B27 individual did not respond to this epitope before or after treatment.
- M41L occurred at anchor positions p2 and p9 in several computer predicted RT epitopes (33-41, 32-41, and 40-49) ([http://bimas.dcrn.nih.gov/molbio/hla\\_bind](http://bimas.dcrn.nih.gov/molbio/hla_bind)), and increased the predicted binding affinity for 6 HLA molecules (B2705, B5102, C3, A0201, B2705 and B3901)

**HXB2 Location** RT (33–41)**Author Location** RT (33–41 MN)**Epitope** ALVEICTEM**Subtype** B**Immunogen** vaccine*Vector/Type:* DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)**Species (MHC)** humanized mouse (A\*0201)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy**References** Isaguliants *et al.* 2004

- Immunization of HLA-A\*0201-transgenic mice with synthetic genes encoding clusters of human A\*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains.
- This was one of five HLA-A\*0201 epitopes from the RT or protease proteins that was included in the polyepitope vaccine. When the transgenic HLA A\*0202 mice were vaccinated with the polyepitope construct or with a mixture of RT peptides, a sustained low level CD8+ T-cell gamma IFN response was observed, in contrast to when an intact RT gene was used for vaccination.

**HXB2 Location** RT (33–41)**Author Location** Pol (132–140 IIIB)**Epitope** ALVEICTEM**Epitope name** pol132-140**Subtype** B**Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade IIIB *HIV component:* Gag-Pol**Species (MHC)** humanized mouse (A\*0201)**Assay type** Intracellular cytokine staining**Keywords** subtype comparisons, vaccine-specific epitope characteristics, immunodominance, variant cross-recognition or cross-neutralization, vaccine antigen design**References** Singh & Barry 2004

- When A\*0201-C3H/J transgenic mice were immunized with plasmids encoding wild-type gag-pol, codon-optimized (CO) gag-pol, and an expression library vaccine expressing 16 fragments of gag-pol fused with ubiquitin for proteasome targeting (ELI), the ELI vaccine produced up to 10-fold higher CD8 T-cell responses than the other two vaccines. In contrast to the wt and CO vaccines, which tended to augment only immunodominant responses, boosting with the ELI vaccine resulted in

many CD8 responses against variant epitopes from different HIV-1 clades, and against drug-resistant variants.

- Different variants of this epitope from different clades were tested. WT and CO vaccines produced low level CD8+ T-cell responses against the B clade form as well as against variants from other clades, but the ELI vaccine produced much more intense responses against the B clade and all variants tested, including after boosting. The variants were: clade A, atTDictem; clade C, atTAicEem; and clade D, alleicSem.

**HXB2 Location** RT (33–41)

**Author Location** Pol

**Epitope** ALVEICTEM

**Epitope name** A9M

**Immunogen** vaccine

*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3

**Species (MHC)** transgenic mouse (A\*0201)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells

**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** RT (33–41)

**Author Location** Pol

**Epitope** ALVEICTEM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.

- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A\*02 restricted epitope, ALVEICTEM was mutated to ALiEICTEM in the daughter D2 isolate.

**HXB2 Location** RT (33–41)

**Author Location** RT (33–41)

**Epitope** ALVEICTEM

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

**HXB2 Location** RT (33–41)

**Author Location** RT (33–41)

**Epitope** ALVEICTEM

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- SLYNTVATL was the dominant A2 epitope recognized in patients with chronic infection, except for Subject 11841 who recognized 5/8 epitopes and who had a dominant A-2 response to ALVEICTEM.

**HXB2 Location** RT (33–41)

**Author Location** RT (33–41)

**Epitope** ALVEICTEM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding

**Keywords** acute/early infection, optimal epitope

**References** Altfeld *et al.* 2005



- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized in chronic infection, and even then was recognized infrequently.

**HXB2 Location** RT (33–41)

**Author Location** RT (33–41)

**Epitope** ALVEICTEM

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Canada

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** mimics

**References** Mason *et al.* 2005

- CTL responses against the human IP-30 signal peptide sequence LLDVPTAAV were shown to be elicited by stimulation of PBMCs from HIV-1 infected individuals with HIV protease peptide 76-84, LVGPTPVNI. In vitro stimulation with HIV PR 76-84 or the IP-30 signal peptide was shown to activate a comparable population of cross-reactive effector cells. None of the peptides activated CTL in non-HIV-infected individuals. IP-30 signal peptide was shown to have lower avidity T-cell interactions than the HIV peptide.
- As a control, responses to A2-restricted HIV epitopes ALVEICTEM, EELRQHLLRW, and LSPRTLNAW were shown not to give IP-30 responses.

**HXB2 Location** RT (33–41)

**Author Location** RT

**Epitope** ALVEICTEM

**Epitope name** A2-AM9(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (33–41)

**Author Location** RT (33–41)

**Epitope** ALVEICTEM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2, A3)

**Country** Canada

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization

**References** Mason *et al.* 2004

- Accumulation of specific antiretroviral drug-resistance mutations in Pol gene was shown to sustain and even enhance the antigenicity and immunogenicity of HIV-1 CTL epitopes in this region. Several different patterns of cross-reactivity and selective recognition of wild-type and variant epitopes were found.
- ALVEICTEI variant is detected due to appearance of M41L resistance mutation. The M41L variant peptide was almost always preferentially recognized by CTLs from patients undergoing antiretroviral therapy.

**HXB2 Location** RT (33–43)

**Author Location** RT (33–43)

**Epitope** ALVEICTEMEK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**References** Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol - RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.
- C. Brander notes that this is an A\*0301 epitope in the 1999 database, G. Haas, pers. comm.

**HXB2 Location** RT (33–43)

**Author Location** RT (33–43)

**Epitope** ALVEICTEMEK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0301 epitope.

**HXB2 Location** RT (33–43)

**Author Location** RT (33–43)

**Epitope** ALVEICTEMEK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

**HXB2 Location** RT (33–43)  
**Author Location** RT Pol (188–198)  
**Epitope** ALVICTEMEK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong T-helper cell responses. Only patients starting with moderately high viral load (VL) were able to reduce the VL set point. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up.
- Less than 2 of 14 patients recognized this epitope.

**HXB2 Location** RT (33–43)  
**Author Location** RT  
**Epitope** ALVEICTEMEK  
**Epitope name** A3-AK11(RT)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (38–52)  
**Author Location** RT (203–209)  
**Epitope** CTEMEKEGKISKIGP  
**Immunogen** vaccine  
*Vector/Type:* Salmonella *HIV component:* RT  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**References** Burnett *et al.* 2000

- A live attenuated bacterial vaccine, Salmonella SL3261-pHART, with an inserted HIV epitope in the Lpp-OmpA-HIV fusion protein, induced a specific CTL response in BALB/c mice (<15% lysis assayed by Cr-release of target cells)

**HXB2 Location** RT (38–52)

**Author Location** RT (205–219 BRU)  
**Epitope** CTEMEKEGKISKIGP  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* RT

**Species (MHC)** mouse (H-2<sup>k</sup>)  
**Keywords** review  
**References** De Groot *et al.* 1991; Menendez-Arias *et al.* 1998

- Murine and human helper and CTL epitope.
- Epitope noted in a review by Menendez-Arias *et al.* [1998] to be located in the "fingers" domain of RT and is a helper and CTL epitope.

**HXB2 Location** RT (38–52)  
**Author Location** RT (205–219)  
**Epitope** CTEMEKEGKISKIGP  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (broad)  
**Keywords** review  
**References** Hosmalin *et al.* 1990; Menendez-Arias *et al.* 1998

- Murine and human helper and CTL epitope.
- Epitope noted in a review by Menendez-Arias *et al.* [1998] to be located in the "fingers" domain of RT and is a helper and CTL epitope.

**HXB2 Location** RT (39–47)  
**Author Location** RT  
**Epitope** TEMEKEGKI

**Immunogen**  
**Species (MHC)** mouse (H-2K<sup>k</sup>)  
**References** Leggatt *et al.* 1998

- Epitope variants were examined for CTL response in concert with H-2K<sup>k</sup> MHC class I binding – all of the following combinations were observed: (i) two single mutations which did not alone abrogate CTL activity did abrogate activity when combined, (ii) loss of recognition of a single substitution could be restored by an additional substitution, and (iii) sometimes there was recognition of two single substitutions as well as the combination of those substitutions.
- 2E and 9I are anchor residues for H-2K<sup>k</sup>—if you have M in the third position, it enhances H-2K<sup>k</sup> binding 10-fold, but polymorphism at this site is important for the overall conformation of the peptide and can influence T cell recognition.

**HXB2 Location** RT (39–47)  
**Author Location** RT (206–214)  
**Epitope** TEMEAEGKI

**Immunogen** in vitro stimulation or selection  
**Species (MHC)** mouse  
**Keywords** TCR usage  
**References** Leggatt *et al.* 1997

- Ala-substituted nonamer-peptide used to test a non-radioactive assay for murine CTL recognition of peptide-MHC class I complexes.
- The new assay is CTL adherence assay (CAA), and is based on the discovery that CTL develop adhesive properties upon TCR triggering.

- Substitutions in TEMEAEGKI that reduce cytolytic activity were correctly detected by CAA.

**HXB2 Location** RT (42–50)  
**Author Location** RT (42–50 LAI)  
**Epitope** EKEGKISKI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5101)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5101 epitope.

**HXB2 Location** RT (42–50)  
**Author Location** RT (42–50 HXB2)  
**Epitope** EKEGKISKI  
**Epitope name** EI9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5101)  
**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape, immune evasion, optimal epitope  
**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

**HXB2 Location** RT (42–50)  
**Author Location** RT (42–50)  
**Epitope** EKEGKISKI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5101)  
**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding  
**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism  
**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naïve individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naïve T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.

- This epitope, EKEGKISKI, was predicted to be restricted by HLA B\*2701, B\*3801, B\*3901, B\*3909, B\*4402, B\*5101, B8.

**HXB2 Location** RT (42–50)  
**Author Location** RT (42–50 LAI)  
**Epitope** EKEGKISKI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**References** Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

**HXB2 Location** RT (42–50)  
**Author Location** RT (42–50)  
**Epitope** EKEGKISKI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** escape  
**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** RT (42–50)  
**Author Location**  
**Epitope** EKEGKISKI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, immunodominance, optimal epitope  
**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.

- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope EKEGKISKI elicited a magnitude of response of 270 SFC with a functional avidity of 0.1nM and binding affinity of 14059nM.

**HXB2 Location** RT (55–72)

**Author Location** (C consensus)

**Epitope** PYNTPVFAIKKKDSTKWR

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (57–65)

**Author Location** RT (57–65)

**Epitope** NTPVFAIKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A0201) HLA-restriction. Thus, CTL response was less degenerate than peptide binding to MHC.
- This epitope, NTPVFAIKK, was predicted to be restricted by HLA A\*0301, A\*6601, C\*0102.

**HXB2 Location** RT (57–65)

**Author Location** RT

**Epitope** NTPVFAIKK

**Immunogen** HIV-1 infection, vaccine

**Species (MHC)** human (A\*6801, A3 superfamily)

**Country** Australia

**Assay type** Intracellular cytokine staining

**Keywords** HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization, optimal epitope

**References** Stratov *et al.* 2005

- CD8 T-cells targeting epitopes spanning drug resistance induced mutations were detected in 3/25 individuals harboring multidrug-resistant HIV-1. Novel CD8 T-cell responses were detected against epitopes with common protease inhibitor fitness mutations. T-cell immunity to drug-resistant variants was confirmed in SHIV-infected macaques, where CD8 and CD4 immune responses to RT and protease resistance mutations were elicited using peptide-based immunotherapy.
- The immune response to this peptide was cross-reactive for both the wild type and RT drug resistance mutation K65R, and NTPVFAIKK and ntpvfaikR stimulated CD8 T-cell responses with equal efficiency. The C-terminal R or K is required for a full response; NTPVFAIK stimulated a much weaker response.
- The 3 people that responded to the drug resistant forms of the virus were among those that had the highest levels of CD4 and CD8 T-cell responses, indicating that they were among the most immunocompetent.

**HXB2 Location** RT (57–65)

**Author Location** Pol (236–244)

**Epitope** NTPVFAIKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** RT (57–66)

**Author Location** Pol

**Epitope** NTPVFAIKKK

**Epitope name** 1274

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** chimpanzee, goat, baboon (A11, A68, B8)

**Donor MHC** A01, A68, B15, B40, Cw03; A25, A68, B18, B27

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, supertype, computational epitope prediction, immunodominance, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC superotypes.
- Estimated binding probability for NTPVFAIKKK:53%. Epitope binds to A11 and A68 supertype, and is immunodominant.

**HXB2 Location** RT (57–66)

**Author Location** Pol (209–221)

**Epitope** NTPVFAIKKK

**Subtype** B

**Immunogen** HIV-1 infection, peptide-HLA interaction

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** immunodominance

**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, NTPVFAIKKK, is similar to human protein HERV, sequence SPwNTPVFvIKKK.

**HXB2 Location** RT (73–82)

**Author Location** RT (73–82)

**Epitope** KLVDFRELNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** RT (73–82)

**Author Location** RT (73–82 LAI)

**Epitope** KLVDFRELNK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Samri *et al.* 2000

- This epitope contains the mutation L74V, a frequent mutation induced by nucleoside reverse transcriptase inhibitors.

- The wild-type, but not the mutated peptide, was recognized before and after zidovudine treatment in A3-restricted patients 252#0 and 252#4.

- Mutation L74V affects the p2 anchor position in RT epitopes and was predicted to reduce binding to A3 ([http://bimas.dert.nih.gov/molbio/hla\\_bind](http://bimas.dert.nih.gov/molbio/hla_bind))

**HXB2 Location** RT (73–82)

**Author Location** RT (228–237)

**Epitope** KLVDFRELNK

**Epitope name** A3-KK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 3/7 individuals began to have detectable responses to this epitope after STI.

**HXB2 Location** RT (73–82)

**Author Location** RT (73–82)

**Epitope** KLVDFRELNK

**Epitope name** A3-KK10 Pol

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response, but in this case the epitope did not vary.

**HXB2 Location** RT (73–82)

**Author Location** Pol

**Epitope** KLVDFRELNK

**Epitope name** 1340

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, A23, B49, B57; A02, A03, B08, B51, Cw01, Cw07; A03, A11, B05, B14, Cw08

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KLVDLFRELNK: 36%.

**HXB2 Location** RT (73–82)

**Author Location** (B consensus)

**Epitope** KLVDLFRELNK

**Epitope name** KK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, B07, Cw7

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** RT (73–82)

**Author Location** RT

**Epitope** KLVDLFRELNK

**Epitope name** A3-KK10(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (87–104)

**Author Location** (C consensus)

**Epitope** FWEVQLGIPHPAGLKKKK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (93–101)

**Author Location** (LAI)

**Epitope** GIPHPAGLK

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*0301)

**Keywords** optimal epitope

**References** Altfeld 2000; Frahm *et al.* 2008

**HXB2 Location** RT (93–101)

**Author Location** RT (248–257)

**Epitope** GIPHPAGLK

**Epitope name** A3-GK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals began to have detectable responses to this epitope after STI.

**HXB2 Location** RT (93–101)

**Author Location** RT (93–101)

**Epitope** GIPHPAGLK

**Epitope name** A3-GK9 Pol

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response, but in this case the epitope did not vary.

**HXB2 Location** RT (93–101)

**Author Location** Pol

**Epitope** GIPHPAGLK

**Epitope name** 1337

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, A23, B49, B57

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for GIPHPAGLK: 20%.

**HXB2 Location** RT (93–101)

**Author Location** (B consensus)

**Epitope** GIPHPAGLK

**Epitope name** GK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, B07, Cw7

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** RT (93–101)

**Author Location** RT

**Epitope** GIPHPAGLK

**Epitope name** A3-GK9(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (93–102)

**Author Location** Pol (240–249 93TH253 subtype CRF01)

**Epitope** GIPHPAGLKK

**Epitope name** P248-257

**Subtype** CRF01\_AE

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers - weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 265 who was HLA A2/A11 and after a second stimulation *in vitro* gave a strong response in HEPS study subject 128 who was HLA A11/A33.

**HXB2 Location** RT (93–102)

**Author Location** Pol (240–249 93TH253 subtype CRF01)

**Epitope** GIPHPAGLKK**Subtype** CRF01\_AE**Immunogen** HIV-1 infection**Species (MHC)** human (A11)**Keywords** subtype comparisons**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it.
- This epitope was highly conserved in other subtypes, and exact matches were common.

**HXB2 Location** RT (98–113)**Author Location** RT (252–266)**Epitope** AGLKKKSVTLVDVGD**Immunogen** HIV-1 infection**Species (MHC)** human (Cw4)**References** Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population.
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs.

**HXB2 Location** RT (98–113)**Author Location** Pol (254–264 BH10, LAI)**Epitope** AGLKKKSVTLVDVGD**Immunogen** HIV-1 infection**Species (MHC)** human**References** Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is GLKKKSVTL) has similarity with the CD166 antigen (activated leukocyte-cell adhesion molecule), fragment GLKKRESLTLI.

**HXB2 Location** RT (102–118)**Author Location** (C consensus)**Epitope** KKSVTLVDVGDYFSV**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0401)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (103–117)**Author Location** RT (257–251)**Epitope** KKSVTVDVGDYFVS**Immunogen** HIV-1 infection**Species (MHC)** human (Cw4)**References** Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune.
- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs.

**HXB2 Location** RT (107–115)**Author Location** RT (262–270 IIIB)**Epitope** TVLDVGDY**Immunogen****Species (MHC)** human (B\*3501)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*3501 epitope.

**HXB2 Location** RT (107–115)**Author Location** Pol (262–270)**Epitope** TVLDVGDY**Epitope name** TY9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*3501)**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay**Keywords** escape, acute/early infection**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this epitope was not evident until month 20, and increased over time.

**HXB2 Location** RT (107–115)**Author Location** RT (107–115)**Epitope** TVLDVGDY**Immunogen** HIV-1 infection**Species (MHC)** human (B\*3501)**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding



**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, TVLDVGDAY, was predicted to be restricted by HLA B0702, B3501, B5102, B5103, B5301, B5401 and B5502 as well. B\*1501, B\*3501, B\*5701, C\*0304.

**HXB2 Location** RT (107–115)

**Author Location** RT (262–270 IIIB)

**Epitope** TVLDVGDAY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** review, responses in children, mother-to-infant transmission

**References** Menendez-Arias *et al.* 1998; Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- TVLDMGDAC is a naturally occurring variant that is less reactive.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope includes a catalytic residue (Asp-110) in the active site of RT.

**HXB2 Location** RT (107–115)

**Author Location** Pol (262–270 IIIB)

**Epitope** TVLDVGDAY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- An additional variant that gave a positive CTL response: TVLDMGDAC.

**HXB2 Location** RT (107–115)

**Author Location** Pol (262–270)

**Epitope** TVLDVGDAY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** RT (107–115)

**Author Location** RT (262–270 SF2)

**Epitope** TVLDVGDAY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 0/1 group 3.

**HXB2 Location** RT (107–115)

**Author Location**

**Epitope** TVLDVGDAY

**Epitope name** Pol-TY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 8/21 (38%) recognized this epitope.

**HXB2 Location** RT (107–115)

**Author Location** Pol

**Epitope** TVLDVGDAY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** A11, A3, B35, B51

**Keywords** mother-to-infant transmission

**References** Sabbaj *et al.* 2002

- IFN $\gamma$  T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested with using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- T-cells in breast milk from a volunteer who was HLA A3, A11, B35, B51 induced IFN $\gamma$  after stimulation with either of two overlapping peptides that carry known B35 epitope TVLDVGDAY.

- The frequencies of responses in the two compartments differed, and 2/4 women that responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

**HXB2 Location** RT (107–115)

**Author Location** RT (107–115)

**Epitope** TVLDVGDAY

**Subtype** AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** Canada

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization

**References** Mason *et al.* 2004

- Accumulation of specific antiretroviral drug-resistance mutations in Pol gene was shown to sustain and even enhance the antigenicity and immunogenicity of HIV-1 CTL epitopes in this region. Several different patterns of cross-reactivity and selective recognition of wild-type and variant epitopes were found.
- TiLDVGDAY, TVLDVGDaf and TiLDVGDaf variants are detected due to appearance of V108I and Y115F resistance mutations. Complete cross-reactivity of wild-type and variant peptides was observed.

**HXB2 Location** RT (107–115)

**Author Location** RT Pol (262–270)

**Epitope** TVLDVGDIY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/9 patients recognized this epitope.

**HXB2 Location** RT (107–115)

**Author Location** RT

**Epitope** TVLDVGDAY

**Epitope name** B35-TY9(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.

- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (108–118)

**Author Location** RT (108–118)

**Epitope** VLDVGDAYFSV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

**HXB2 Location** RT (108–118)

**Author Location** RT (108–118)

**Epitope** VLDVGDAYFSV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning

the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.

- This epitope, VLDVGDAYFSV, was detected within overlapping peptide KKKSVTVLDVGDAYFSV.

**HXB2 Location** RT (108–118)

**Author Location** RT (267–277)

**Epitope** VLDVGDAYFSV

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (A\*0201)

**References** van der Burg *et al.* 1996

- High dissociation rate, but immunogenic in primary CTL induction after repeated stimulations with peptide.
- CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual.

**HXB2 Location** RT (108–118)

**Author Location** Pol

**Epitope** VLDVGDAYFSV

**Epitope name** V11V

**Immunogen** vaccine

*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3

**Species (MHC)** transgenic mouse (A\*0201)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells

**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** RT (108–118)

**Author Location** RT (267–277)

**Epitope** VLDVGDAYFSV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** dendritic cells

**References** Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.

- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.

- VLDVGDAYFSV is a conserved HLA-A2 epitope included in this study – 4/6 patients had this sequence as their HIV direct sequence, but only one of these had a detectable CTL response – the other two had the sequences EEDVGDAYFSV and EL-DVGDAYFSV and no detectable CTL response.

**HXB2 Location** RT (108–118)

**Author Location** RT (267–277)

**Epitope** VLDVGDAYFSV

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (A2)

**References** van der Burg *et al.* 1995

- Binds HLA-A\*0201 – CTL generated by *in vitro* stimulation of PBMC from an HIV negative donor.
- VLDVGDAYFSV is in a functional domain.

**HXB2 Location** RT (108–118)

**Author Location** RT Pol (263–273)

**Epitope** VLDVGDAYFSV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 19 patients recognized this epitope.

**HXB2 Location** RT (108–118)

**Author Location** Pol (263–273)

**Epitope** VLDVGDAYFSV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A2)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** RT (108–122)

**Author Location** RT (257–251)

**Epitope** VLDVGDAYFSVPLDE

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw4)

**References** Bernard *et al.* 1998

- This study focuses on six rare long-term survivor HIV-infected people who were infected for many years without exhibiting immune dysregulation – such immunologically normal HIV-infected (INHI) cases occur at a frequency between 0.1 and 1% in the infected population.

- No direct CTL were found in any of the six INHIs, but above background CTLp activity was founded in 3/6 INHIs.

**HXB2 Location** RT (113–120)

**Author Location** Pol (268–275 SF2)

**Epitope** DAYFSVPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24, B\*5101)

**Keywords** subtype comparisons, rate of progression

**References** Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA -B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996; Lancet 22:1187, 1986; Hum Immunol 22:73, 1988; Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B\*5101 anchor residues, 33 bound to HLA-B\*5101, seven of these peptides were reactive with CTL from 3 B\*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences, DAYFSVPL is conserved.

**HXB2 Location** RT (113–120)

**Author Location** RT (113–120)

**Epitope** DAYFSVPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** RT (116–124)

**Author Location** (C consensus)

**Epitope** FSVPLDEDF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- Mutational patterns in the E7 residue of FSVPLDEDF are associated with the presence of the HLA presenting molecule in the host.

- FSVPLDEDF not optimized.

**HXB2 Location** RT (116–124)

**Author Location** (C consensus)

**Epitope** FSVPLDEDF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5702)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- FSVPLDEDF is an optimal epitope.

**HXB2 Location** RT (116–124)

**Author Location** (C consensus)

**Epitope** FSVPLDEDF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5703)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- FSVPLDEDF is an optimal epitope.

**HXB2 Location** RT (116–135)

**Author Location** Pol (271–290)

**Epitope** FSVPLDEDFRKYTAFTIPSI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.

- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.

- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** RT (117–126)  
**Author Location** Pol (264–273 93TH253 subtype CRF01)  
**Epitope** SVPLDESFRRK  
**Epitope name** P272-281  
**Subtype** CRF01\_AE  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (A11)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope after a second stimulation *in vitro* gave a strong response in HEPS study subject 128 who was HLA A11/A33.

**HXB2 Location** RT (117–126)  
**Author Location** Pol (264–273 93TH253 subtype CRF01)  
**Epitope** SVPLDESFRRK  
**Subtype** CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Keywords** subtype comparisons  
**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 3/8 tested FSWs recognized it.
- This epitope was only conserved in CRF01, and subtype A and B, and exact matches were uncommon.

**HXB2 Location** RT (118–127)  
**Author Location** (C consensus)  
**Epitope** VPLDEDFRKY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*35)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** RT (118–127)  
**Author Location** RT (273–282 SF2)  
**Epitope** VPLDKDFRKY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**Keywords** review  
**References** Menendez-Arias *et al.* 1998; Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- 4/7 B35-positive individuals had a CTL response to this epitope.
- A K to E substitution at position 5 abrogates specific lysis, and reduces binding to B\*3501.
- Menendez-Arias *et al.* [1998], in a review, notes that a Glu to Lys (E to K) change abrogates CTL activity, but that both VPLDEDFRKY and VPLDKDFRKY can serve as HLA-B35 epitopes, so the change must alter T cell receptor binding – residues in this epitope may be important for polymerase activity.

**HXB2 Location** RT (118–127)  
**Author Location** RT (273–282 IIIB)  
**Epitope** VPLDEDFRKY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*3501 epitope.

**HXB2 Location** RT (118–127)  
**Author Location** Pol (273–282)  
**Epitope** VPLDKDFRKY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**References** Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B\*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

**HXB2 Location** RT (118–127)  
**Author Location** (SF2)  
**Epitope** VPLDEDFRKY  
**Epitope name** HIV-B3501-SF2-4  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**References** Tomiyama *et al.* 2000b

- B\*3501 VPLDEDFRKY tetramer binding did not inhibit CTL activity of a clone that react with both HLA-B\*3501 than HLA-B\*5101 presentation of the epitope IPLTEEAEL.

**HXB2 Location** RT (118–127)

**Author Location** RT (118–127)

**Epitope** VPLDEDFRKY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**Donor MHC** A\*2301, B\*1503, B\*3501, Cw2, Cw7

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15–92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** RT (118–127)

**Author Location** Pol (273–282)

**Epitope** VPLDEDFRKY

**Epitope name** VY10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** escape, acute/early infection

**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.

- The response to this epitope was not detected until month 25, and increased over time.

**HXB2 Location** RT (118–127)

**Author Location** RT (273–282 IIIB)

**Epitope** VPLDEDFRKY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501, B35)

**References** Shiga *et al.* 1996

- Binds HLA-B\*3501.

**HXB2 Location** RT (118–127)

**Author Location** (SF2)

**Epitope** VPLDKDFRKY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** binding affinity, rate of progression, escape

**References** Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals – only one of these reduced the binding of the peptide to B35 and was shown to be an escape mutation.
- —E— was found in 8/10 of the B35+ individuals, and three of the B35- individuals – the D → E substituted peptide had similar binding affinity to B35 and was equally susceptible to a CTL clone.

**HXB2 Location** RT (118–127)

**Author Location** RT (273–282 IIIB)

**Epitope** VPLDEDFRKY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** subtype comparisons

**References** Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by three lab workers accidentally infected with HIV-1 IIIB.
- VPLDKDFRKY, a variant found in HIV MN, was not recognized.
- VPHDEDFRKY, a variant found in HIV YU2, was not recognized.
- This epitope was type-specific and conserved in only one other B subtype sequence.

**HXB2 Location** RT (118–127)

**Author Location** RT (273–282 SF2)

**Epitope** VPLDEDFRKY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.

- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 1/1 group 3.

**HXB2 Location** RT (118–127)

**Author Location**

**Epitope** VPLDEDFRKY

**Epitope name** Pol-VY10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 5/21 (24%) recognized this epitope.

**HXB2 Location** RT (118–127)

**Author Location** RT Pol (273–282)

**Epitope** VPLDEDFRKY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/9 patients recognized this epitope.

**HXB2 Location** RT (118–127)

**Author Location** RT

**Epitope** VPLDEDFRKY

**Epitope name** B35-VY10(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (126–135)

**Author Location** RT (293–302 HXB)

**Epitope** KYTAFITPSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART

**References** Shankar *et al.* 1998

- A novel CTL clone was defined with a panel of recombinant vaccinia-RT-infected B-LCL target cells using PBMCs donated by a patient who was HIV-seropositive for 6 years and had not received any antiretroviral therapy.
- There is evidence that some CTL epitopes are poorly presented on the surface of infected cells, but this RT epitope was recognized as effectively on HIV-infected cells as on peptide-pulsed targets.

**HXB2 Location** RT (127–135)

**Author Location** (C consensus)

**Epitope** YTAFTIPSI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YTAFTIPSI is an optimal epitope.

**HXB2 Location** RT (127–135)

**Author Location** Pol

**Epitope** YTAFTIPSV

**Epitope name** YV-9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A02)

**Assay type** Other

**Keywords** escape, TCR usage, immune evasion

**References** Yu *et al.* 2007b

- The dependence of TCR clonotype recruitment on genetic background was determined by studying monozygotic twins infected with the same HIV-1 strain. After an early, initial correlation in the magnitude, specificity and immunodominance of CTL response [Draenert *et al.* J. Exp. Med. 203:529-539(2006)], subsequent disease was mixed with respect to CTL epitopes' mutational escape. TCR alpha and beta chain

repertoires were analyzed and it was found that their clonotypes in HIV-specific CTLs were broadly heterogeneous for both concordant and discordant epitope sequence evolution between the twins. Therefore initial TCR recruitment appears to be an entirely random process independent of genetic background of the infected individual.

- This epitope, YV9, showed discordant epitope evolution between the twins, and both alpha and beta TCR chains recruited were entirely different between them.

**HXB2 Location** RT (127–135)

**Author Location** Pol (316–)

**Epitope** YTAFTIPSI

**Epitope name** Pol-316

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** binding affinity, subtype comparisons, super-type, computational epitope prediction

**References** Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- 2/22 individuals with chronic HIV-1 infection recognized this epitope in ELISPOT.
- 0/12 acutely infected individuals recognized this epitope.
- YTAFTIPSI binds to five HLA-A2 supertype alleles: A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802 (highest affinity)

**HXB2 Location** RT (127–135)

**Author Location** RT (127–135)

**Epitope** YTAFTIPSV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** RT (127–135)

**Author Location** RT (127–135)

**Epitope** YTAFTIPSI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding

**Keywords** acute/early infection, optimal epitope

**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection.

**HXB2 Location** RT (127–135)

**Author Location** RT

**Epitope** YTAFTIPSI

**Epitope name** A2-YI9(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (127–135)

**Author Location** RT

**Epitope** YTAFTIPSI

**Epitope name** A2-YI9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A2, A68, B14, B44, Cw5, Cw8

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape, acute/early infection, antibody generation, co-receptor, immune evasion

**References** Streeck *et al.* 2007b

- A subject with acute and rapid disease progression to AIDS showed no neutralizing antibody activity and rapid decline in HIV-specific CTL response by 6 months post-infection. Virus from this rapid progressor was resistant to neutralization by plasma from a long-term progressor. Viral epitopes did not vary much. This suggests viral immune evasion in the absence of viral sequence variation.
- This epitope, YTAFTIPSI, elicited the dominant CTL response, detectable until 4 months post-infection. YI9 and its flanking sequences FRKYTAFTIPSINNE did not show any escape mutations.

**HXB2 Location** RT (127–135)

**Author Location** Pol (282–290)

**Epitope** YTAFTIPSV

**Epitope name** YV9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)



**Donor MHC** A\*0201, A\*2402, B\*4001, B\*5001, Cw03, Cw04

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization

**References** Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, YTAFTIPSV (YV9) was restricted by HLA-A02. A variant that arose was YTAFTIPSi.

**HXB2 Location** RT (127–135)

**Author Location** Pol (306–314)

**Epitope** YTAFTIPSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 superotypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802)

**HXB2 Location** RT (128–135)

**Author Location** Pol (283–290)

**Epitope** TAFTIPSI

**Epitope name** TI8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** escape, acute/early infection, characterizing CD8+ T cells

**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this epitope was weak and sporadic.

**HXB2 Location** RT (128–135)

**Author Location**

**Epitope** TAFTIPSI

**Epitope name** Pol-TI8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0217, B\*5101)

**Donor MHC** 01RCH46: A\*0201, A\*0217, B\*0801, B\*4002, Cw\*0303, Cw\*0701

**Keywords** HAART, ART

**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Patient 01RCH46 was Hispanic, on HAART, and had a viral load of 21000 and CD4 count of 623 – she also recognized GELDRWEKI, p17(11-19), HLA B\*4002, and KETINEEAA p24(70-78), HLA B\*4002.
- Among HIV+ individuals who carried HLA A\*02, 7/36 (19%) recognized this epitope, two of which also carried B\*5101 which can also restrict this epitope.

**HXB2 Location** RT (128–135)

**Author Location** Pol

**Epitope** TAFTIPSI

**Epitope name** TI8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*51)

**Country** Switzerland

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** rate of progression, HLA associated polymorphism

**References** Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than "other" HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by "other", non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.

- Patients with higher proportions of mutated epitopes also showed lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- TAFTIPSI escapes very soon after seroconversion to the variant TAFTIPSt with change at its carboxyl terminus, position 8, which has been identified by phylogenetic analysis to be under strong positive selection pressure. It was present in 7/8 of HLA-matched patients and 21/57 of HLA-unmatched patients.

**HXB2 Location** RT (128–135)

**Author Location** RT (295–302 IIB)

**Epitope** TAFTIPSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5101)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5101 epitope.

**HXB2 Location** RT (128–135)

**Author Location** Pol (283–290 SF2)

**Epitope** TAFTIPSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5101)

**Keywords** subtype comparisons, rate of progression

**References** Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996; Lancet 22:1187, 1986; Hum Immunol 22:73, 1988; Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B\*5101 anchor residues, 33 bound to HLA-B\*5101, seven of these peptides were reactive with CTL from 3 B\*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences, but TAFTIPSI is somewhat variable.

**HXB2 Location** RT (128–135)

**Author Location** RT (295–302)

**Epitope** TAFTIPSI

**Epitope name** P5

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5101)

**Keywords** HAART, ART, escape

**References** Samri *et al.* 2000

- The epitope TAFTIPSI was recognized by patient 246#1 in a study of the effects of therapy escape mutations on CTL recognition.

**HXB2 Location** RT (128–135)

**Author Location** RT (128–135 IIB)

**Epitope** TAFTIPSI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5101)

**Keywords** epitope processing, escape

**References** Moore *et al.* 2002b

- HIV polymorphisms in the RT protein were examined relation to HLA alleles found in a population of 473 participants in the Western Australian HIV Cohort Study. 64 significant associations between polymorphisms at particular positions and HLA alleles were detected, for HLA-B7, -B12, -B35 and -B15. Fifteen of these were in positions with known epitopes, 4 in anchor residues, 11 in other positions. Six additional polymorphic sites associated with particular HLA molecules flanked known epitopes and may relate to processing.
- TAFTIPSI was one of two epitopes characterized in detail. C-terminal I135x substitutions were associated with people who carried HLA-B5 – 39/40 (98%) of HLA-B\*5101 individuals had substitutions in this position, while only 127/431 (29%) who did not have HLA-B\*5101 did. The predominant substitution was kytaftipsT, and this mutation is predicted to abrogate binding to HLA-B\*5101.

**HXB2 Location** RT (128–135)

**Author Location** RT (128–135 HXB2)

**Epitope** TAFTIPSI

**Epitope name** TI8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5101)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Last position (8) of the epitope had potentially experienced positive selection. TAFTIPSt, TAFTIPSt and TAFTIPStv escape variants were found.

**HXB2 Location** RT (128–135)

**Author Location** Pol (283–288 NL-432)

**Epitope** TAFTIPSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5101)

**Assay type** Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay, CTL suppression of replication

**Keywords** binding affinity, class I down-regulation by Nef, rate of progression

**References** Tomiyama *et al.* 2005

- HLA-B\*5101 associated with slow progression to the disease state was studied as related to Nef-mediated HLA class I downregulation. It was shown that different CTLs have different ranges of ability to kill HIV-1 infected CD4+ T cells and suppress HIV-1 replication. This was found to be a function

of the specific HIV-1 epitope presented by the corresponding HLA allele to the CTL.

- Certain epitope recognising CTL clones or lines were therefore, capable of killing HIV-1 infected cells even in the presence of Nef-mediated MHC 1 downregulation, while other CTL clones recognising different epitopes were not so capable.
- There was no significant difference in cytokine production or cytokine producing cells between CTLs that were capable of killing CD4+ T-cells infected with HIV-1 and those CTLs that could not kill such HIV-1 infected cells.
- On the basis of studies involving binding abilities and cytolytic activities for four different epitopes that correlate with HLA-B\*5101-restricted CTLs, it is suggested that the ability of CTLs to kill infected CD4+ T cells is due to the number of epitopes presented by the HLA on the surface of the CD4+ T cells rather than the ability of TCR to recognise the epitope.

**HXB2 Location** RT (128–135)

**Author Location** RT (295–302 IIIB)

**Epitope** TAFTIPSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Keywords** review

**References** Menendez-Arias *et al.* 1998; Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- TAFTIPST, a variant found in HIV-1 CAM1, was also recognized but 100-fold more peptide was needed.
- TAFTIPSV, a variant found in HIV-1 VE1RT, was also recognized, but 10-fold more peptide was needed.
- TVFTIPSI, a variant found in HIV-1 MANC, was also recognized.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope includes a region near the active site of RT – the substitution of the position two conservative change from A to V decreases CTL recognition.

**HXB2 Location** RT (128–135)

**Author Location** RT (295–302)

**Epitope** TAFTIPSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- Three of the four individuals that responded to SLYNTVATL recognized additional HIV epitopes, and all three were also HLA B51 and recognized this epitope as well as other epitopes.

**HXB2 Location** RT (128–135)

**Author Location** RT (295–302)

**Epitope** TAFTIPSI

**Epitope name** TAF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Keywords** HAART, ART, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B51+

**HXB2 Location** RT (128–135)

**Author Location** RT (295–302 LAI)

**Epitope** TAFTIPSI

**Epitope name** P5

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Keywords** HAART, ART

**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** RT (128–135)

**Author Location** Pol

**Epitope** TAFTIPSI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A11, A3, B35, B51

**Keywords** mother-to-infant transmission

**References** Sabbaj *et al.* 2002

- IFN $\gamma$  T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested with using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- T-cells in breast milk from a volunteer who was HLA A3, A11, B35, B51 induced IFN $\gamma$  after stimulation with either of two overlapping peptides that carry known B51 epitope TAFTIPSI.

- The frequencies of responses in the two compartments differed, and 2/4 women that responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

**HXB2 Location** RT (128–135)

**Author Location** RT (128–135)

**Epitope** TAFTIPSI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A\*0201, A11, B51, B61, Cw\*14, Cw2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** RT (128–135)

**Author Location** RT (128–135)

**Epitope** TAFTIPSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 5 epitopes from this individual that varied over time where the internal mutations became fixed; a dramatic decrease in CTL activity against the wild type epitope was observed as the mutation arose. The taftipsT variant residue found at 47 months postseroconversion.

**HXB2 Location** RT (128–135)

**Author Location** Pol

**Epitope** TAFTIPSI

**Epitope name** TI8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 8, taftipsT, was found in the most polymorphic residue in the epitope. This was shared between clades B and C.

**HXB2 Location** RT (128–135)

**Author Location** Pol (295–302)

**Epitope** TAFTIPSI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A2, A31, B51, B58w4

**Country** United States

**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, escape, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells

**References** Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied. This epitope provided the best evidence for apparent immune escape during HAART.
- Prior to the initiation of therapy, taftipsT variant was found in 24/24 clones. At week 14 of therapy, this variant was completely replaced with taftipsI. By week 19, a complete replacement occurred again, this time to taftipsM. The change at nucleotide level suggests a stepwise progression from ACA to ATA to ATG.
- The taftipsT and taftipsM variants had lower avidity than the taftipsI variant, but this wasn't evident at saturating conditions; only careful titrations revealed the difference. HLA-B51 stabilization studies revealed the increased stabilization with the taftipsI form. Also, CD3 down-regulation was larger in response to taftipsI.
- The viral shift to the taftipsM variant during HAART was predicted to have minimal or undetectable effect on drug sensitivity.

**HXB2 Location** RT (128–135)

**Author Location** RT

**Epitope** TAFTIPSI

**Epitope name** B51-TI8(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (128–135)

**Author Location**

**Epitope** TAFTIPSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B51), 2 additional HLAs (B35, B40) were statistically predicted to be associated with this epitope.

**HXB2 Location** RT (128–135)

**Author Location** RT Pol (128–135)

**Epitope** TAFTIPSI

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A3, A32, B15, B51

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in

vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.

- The best estimate of escape rate for this epitope, YF-PDWQDYT, was found to be 0.002/day (optimistic escape rate = 0.012), with SE of 0.001.
- In the subject studied, the monotonic outgrowth of a I290T mutation in Pol was observed over a period of 817 days.

**HXB2 Location** RT (130–144)

**Author Location** RT (130–144)

**Epitope** FTIPSPINNETPGIRY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A25)

**Assay type** Chromium-release assay

**Keywords** assay standardization/improvement

**References** Lubong *et al.* 2004

- Using IL7 or IL15 in culturing of HIV-1-specific CTL clones was inferior to using IL-2 alone; the addition of these cytokines to IL-2 did not show any advantage. Neither proliferation, survival, nor lytic capacity of HIV-1-specific CTLs was significantly enhanced by addition of IL7 or IL15.

**HXB2 Location** RT (136–144)

**Author Location** RT (136–144 HXB2)

**Epitope** NNETPGVRY

**Epitope name** NY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1801)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- NNETPGiRY, NsETPGVRY, NNEiPGVRY, NNEiPGiRY, NNngTPGVRY and NNEvPGiRY escape variants were found.

**HXB2 Location** RT (137–146)

**Author Location** (C consensus)

**Epitope** NETPGIRYQY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*18)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the E2 residue of NETPGIRYQY are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** RT (137–146)

**Author Location**

**Epitope** NETPGIRYQY

**Epitope name** NY10

**Immunogen**

**Species (MHC)** human (B18)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B18 epitope.

**HXB2 Location** RT (142–149)

**Author Location** (C consensus)

**Epitope** IRYQYNVL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1401)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- IRYQYNVL is an optimal epitope.

**HXB2 Location** RT (142–149)

**Author Location**

**Epitope** IRYQYNVL

**Epitope name** IL9

**Immunogen**

**Species (MHC)** human (B\*1401)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1401 epitope.

**HXB2 Location** RT (149–159)

**Author Location** (C consensus)

**Epitope** LPQGWKGSPAI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3910)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- LPQGWKGSPAI is an optimal epitope.

**HXB2 Location** RT (151–159)

**Author Location** Pol (306–314 SF2)

**Epitope** QGWKGSPAI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5101)

**Keywords** subtype comparisons, rate of progression

**References** Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS.
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B\*5101 anchor residues, 33 bound to HLA-B\*5101, seven of these peptides were reactive with CTL from 3 B\*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences, QGWKGSPAI is conserved.

**HXB2 Location** RT (151–168)

**Author Location** RT (151–168 HXB2)

**Epitope** QGWKGSPAI FQSSMTKIL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** RT (153–165)  
**Author Location** RT (308–320)  
**Epitope** WKGSPAIFQSSMT  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** responses in children, mother-to-infant transmission  
**References** Brander & Walker 1995

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

**HXB2 Location** RT (153–165)  
**Author Location** Pol (308–320)  
**Epitope** WKGSPAIFQSSMT  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** RT (153–167)  
**Author Location** RT (SF2)  
**Epitope** WKGSPAIFQSSMTKI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Altfield *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- RT peptides SQIYPGIKVRQLCKL and WKGSPAIFQSSMTKI were recognized.

**HXB2 Location** RT (156–164)  
**Author Location** RT (156–164)  
**Epitope** SPAIFQSSM  
**Epitope name** SM9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0702)  
**Country** United Kingdom  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** epitope processing, computational epitope prediction, escape  
**References** Zimbwa *et al.* 2007

- E169D is a processing mutation for HLA-B\*0702 restricted SPAIFQSSM (SM9) as well as an epitope variation for HLA-A\*0301 restricted MTKILEPFR (MR9).
- CTL recognition of SM9 was detected 5 days post-infection with wild type (169E) HIV-1, but not with mutant 169D virus.
- Mutation 169D is five residues downstream of SM9. In vitro proteasome processing assays showed that the 27-mer synthetic peptide QGWKGSIPAIFQSSMTKILEPFRKQNPd released intermediate peptide QGWKGSIPAIFQSSM within 6 h. Mutant peptide QGWKGSIPAIFQSSMTKILdPFRKQNPd did not release this SM9-appropriate intermediate.

**HXB2 Location** RT (156–164)  
**Author Location** RT (156–164)  
**Epitope** SPAIFQSSM  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*07)  
**Assay type** Other  
**Keywords** HLA associated polymorphism  
**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- SPAIFQSSM was a previously defined B\*07 presented epitope that encompassed a B\*0702-associated polymorphism, SPAIFQsSM, in the seventh position.

**HXB2 Location** RT (156–164)  
**Author Location** RT (156–164)  
**Epitope** SPAIFQSSM  
**Epitope name** SM9  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702, B\*8101)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other  
**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism  
**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction
- Only B\*0702 was found to be associated with polymorphism.

**HXB2 Location** RT (156–164)  
**Author Location** RT (311–319 SF2)  
**Epitope** SPAIFQSSM  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**Keywords** review

**References** Menendez-Arias *et al.* 1998; Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- Only 1/7 B35-positive individuals had a CTL response to this epitope.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope is near the active site of RT.

**HXB2 Location** RT (156–164)

**Author Location** (C consensus)

**Epitope** SPAIFQSSM

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4202)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- SPAIFQSSM is an optimal epitope.

**HXB2 Location** RT (156–164)

**Author Location** (C consensus)

**Epitope** SPAIFQSSM

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702, B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** RT (156–164)

**Author Location** RT (311–319 SF2)

**Epitope** SPAIFQSSM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** review

**References** Menendez-Arias *et al.* 1998; Shiga *et al.* 1996

- Binds HLA-B\*3501.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope includes catalytic residues in the active site of RT.

**HXB2 Location** RT (156–164)

**Author Location** Pol (311–319)

**Epitope** SPAIFQSSM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** RT (156–164)

**Author Location** RT Pol (311–319)

**Epitope** SPAIFQSSM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/9 patients recognized this epitope.

**HXB2 Location** RT (156–164)

**Author Location** Pol (156–164 HXB2)

**Epitope** SPAIFQSSM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, immunodominance

**References** Hay *et al.* 1999

- CTL response to IPRRIRQGL was the immunodominant response in a rapid progressor – there was a subdominant response to SPAIFQSSM in Pol, and interestingly, no response to commonly immunodominant HLA A\*0201 epitope SLYNTVATL, although this individual was HLA A\*0201.
- The individual showed a strong initial CTL response at the time of the initial drop in viremia, but it was quickly lost, although memory cells persisted.
- Despite the initial narrow response to two epitopes, no other CTL responses developed.
- No HIV-specific lymphoproliferative responses were detected in this patient, and neutralizing antibody response was weak.
- Variants of this epitopes were observed *in vivo* (spaifqCsm, spSifqssm), but the binding motifs for B7 were preserved (P2, and C-term aromatic or hydrophobic)

**HXB2 Location** RT (156–164)

**Author Location** Pol

**Epitope** SPAIFQSSM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, acute/early infection

**References** Islam *et al.* 2001



- Subject 053i was followed longitudinally from acute infection through death, and had rapid progression to AIDS.
- This individual had a dominant response to IPRRIRQGL with strong *in vivo* activated responses and *in vitro* stimulated memory responses and a subdominant response to SPAIFQSSM – during the course of disease progression (4 Years), the functional CTL responses were lost and no sequence variation occurred with in both epitopes, but CTL clones specific for IPRRIRQGL persisted throughout.

**HXB2 Location** RT (156–164)

**Author Location** RT (323–331 SF2)

**Epitope** SPAIFQSSM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3.

**HXB2 Location** RT (156–164)

**Author Location** RT (156–164)

**Epitope** SPAIFQSSM

**Epitope name** B7-SM9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 3/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** RT (156–164)

**Author Location** RT (156–164)

**Epitope** SPAIFQSSM

**Epitope name** B7-SM9 Pol

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response; this epitope did not vary.

**HXB2 Location** RT (156–164)

**Author Location**

**Epitope** SPAIFQSSM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** assay standardization/improvement, epitope processing

**References** Draenert *et al.* 2004a

- 96% of optimally defined epitopes have one of only nine amino acids serving as the C-terminal anchor position. Seven amino acids are never found in this position and four are only present in 4% of cases. CD8 T-cell response to an epitope is shown to be best detected when the epitope is situated at the C-terminal end of a longer peptide, and authors suggest that Elispot reagents would be better designed if peptides ended on known C-terminal anchors.
- SPAIFQSSM is suggested to be the optimal epitope instead of SPAIFQSSMT.

**HXB2 Location** RT (156–164)

**Author Location** (B consensus)

**Epitope** SPAIFQSSM

**Epitope name** SM9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A03, B07, Cw7

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between

HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.

- 1/9 individuals recognized this epitope.

**HXB2 Location** RT (156–164)

**Author Location** Pol

**Epitope** SPAIFQSSM

**Epitope name** SM9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 7, spaifqCsm, was found in the most polymorphic residue in the epitope. This was shared between clades B and C.

**HXB2 Location** RT (156–164)

**Author Location** Pol (312–320)

**Epitope** SPAIFQSSM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** RT (156–164)

**Author Location**

**Epitope** SPAIFQSSM

**Epitope name** SM9

**Immunogen**

**Species (MHC)** human (B7)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B07 epitope.

**HXB2 Location** RT (156–164)

**Author Location** RT

**Epitope** SPAIFQSSM

**Epitope name** B7-SM9(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (156–165)

**Author Location** RT (311–319 LAI)

**Epitope** SPAIFQSSMT

**Epitope name** P4

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** HAART, ART, escape

**References** Samri *et al.* 2000

- This epitope contains the mutation P157S which can be induced by nucleoside reverse transcriptase inhibitors.
- It was recognized by patient 252#0 in a study of the effects of therapy escape mutations on CTL recognition.

**HXB2 Location** RT (156–165)

**Author Location** RT (311–319 SF2)

**Epitope** SPAIFQSSMT

**Immunogen**

**Species (MHC)** human (B7)

**Keywords** review

**References** Brander & Walker 1997; Menendez-Arias *et al.* 1998

- Pers. comm. from C. Hey and D. Ruhl to C. Brander and B. Walker.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope includes catalytic residues in the active site of RT.

**HXB2 Location** RT (156–165)

**Author Location** RT (311–319 SF2)

**Epitope** SPAIFQSSMT

**Epitope name** P4

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** HAART, ART

**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.

- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** RT (156–165)

**Author Location** Pol

**Epitope** SPAIFQSSMT

**Immunogen**

**Species (MHC)** human (B7)

**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFN $\gamma$  production in an ELISPOT assay.
- SPAIFQSSMT was confirmed as a previously identified HLA-B7 epitope in this study.

**HXB2 Location** RT (156–165)

**Author Location** RT (III B)

**Epitope** SPAIFQSSMT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** epitope processing, escape

**References** Moore *et al.* 2002b

- HIV polymorphisms in the RT protein were examined relation to HLA alleles found in a population of 473 participants in the Western Australian HIV Cohort Study. 64 significant associations between polymorphisms at particular positions and HLA alleles were detected, for HLA-B7, -B12, -B35 and -B15. Fifteen of these were in positions with known epitopes, 4 in anchor residues, 11 in other positions. Six additional polymorphic sites associated with particular HLA molecules flanked known epitopes and may relate to processing.
- HLA-B7+ individuals with a S162x (18/33) substitution had higher viral loads than those that did not, suggesting escape was associated with diminished immune control of viremia.

**HXB2 Location** RT (156–165)

**Author Location** Pol

**Epitope** SPAIFQSSMT

**Epitope name** 1306

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A03, A24, B07, B38, Cw07, Cw12/13

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for SPAIFQSSMT: 13%

**HXB2 Location** RT (156–165)

**Author Location** RT Pol (311–319)

**Epitope** SPAIFQSSMT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/7 patients recognized this epitope.

**HXB2 Location** RT (158–166)

**Author Location** RT (325–333)

**Epitope** AIFQSSMTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** responses in children, mother-to-infant transmission

**References** Brander & Walker 1995

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

**HXB2 Location** RT (158–166)

**Author Location** RT (325–333 LAI)

**Epitope** AIFQSSMTK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0301 epitope.

**HXB2 Location** RT (158–166)

**Author Location**

**Epitope** AIFQSSMTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** acute/early infection

**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWILGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIQY, B35-PIIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** RT (158–166)

**Author Location** RT (325–333)

**Epitope** AIFQSSMTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A3 and reacted with this epitope as well as two other A3.1 epitopes.

**HXB2 Location** RT (158–166)

**Author Location** RT

**Epitope** AIFQSSMTK

**Immunogen**

**Species (MHC)** human (A\*0301)

**References** Zimbwa *et al.* 2007

- E169D is a processing mutation for HLA-B\*0702 restricted SPAIFQSSM (SM9) as well as an epitope variation for HLA-A\*0301 restricted MTKILEPFR (MR9).
- Mutation 169D lies outside AIFQSSMTK. In vitro proteasome processing assays showed that both wild type or variant 27-mer synthetic peptide QGWKGSPIAFQSSMTK-ILE(d)PFRKQNPd released appropriate AIFQSSMTK-intermediate peptides within 6 h.

**HXB2 Location** RT (158–166)

**Author Location** Pol

**Epitope** AIFQSSMTK

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human, macaque (A\*0301, A11, A33)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** RT (158–166)

**Author Location** RT (325–333 LAI)

**Epitope** AIFQSSMTK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*1101 epitope.

**HXB2 Location** RT (158–166)

**Author Location** Pol (313–321)

**Epitope** AIFQSSMTK

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** subtype comparisons

**References** Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A\*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A\*1101 epitopes was recognized in a clade specific manner. Two other HLA A\*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- AIFQSSMTK is commonly found in viruses representing subtypes A-E. It was strongly recognized by CTL from 2/5 B clade infected Japanese subjects, and 5/6 E clade infected Thai subjects.

**HXB2 Location** RT (158–166)

**Author Location** RT (313–321)**Epitope** AIFQSSMTK**Subtype** B, CRF01\_AE**Immunogen****Species (MHC)** human (A\*1101)**Country** Thailand**Keywords** HIV exposed persistently seronegative (HEPS), structure**References** Li & Bouvier 2004

- HLA-A\*1101 has been associated with resistance to acquisition of HIV-1 infection in female sex-workers in Thailand. Its crystal structure has been determined in association with two immunodominant A\*1101 HIV-1 CTL epitopes. Its anchor residues are confirmed as P2(Ile/Val) and C-term (Lys). The backbone conformation of the peptides is defined as two bulges separated by a secondary anchor residue (P6 Ser or Met) that may offer various advantages in the selection and presentation of CTL epitopes by HLA-A\*1101.

**HXB2 Location** RT (158–166)**Author Location** RT (325–333)**Epitope** AIFQSSMTK**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301, A\*1101, A\*6801, A3)**References** Menendez-Arias *et al.* 1998; Threlkeld *et al.* 1997

- Study of the fine specificity of an A3-like super-type epitope (the A3 super-type includes A\*0301, A\*1101, A\*3101, A\*3301, and A\*6801)
- A3 super-type is characterized by a hydrophobic or hydroxyl containing anchor residue at position 2, and a positive charge in the C-term position.
- While most lines were specific, promiscuous cloned CTL lines were also derived from HIV+ donors that could recognize epitope presented by either A3 or A11 or A\*6801.
- Alanine substitutions throughout the epitope and natural variants indicate that the same amino acid positions are critical for presentation by either MHC molecule, A3 or A11.
- AIFQSSMTK is presented by three members of the A3 superfamily: A\*0301, A\*1101, and A\*6801, and the naturally occurring variants A1S and K9R are recognized with similar efficiency to wild type epitope – AIFQRSMTK can also bind to two additional members of the A3 superfamily, A\*3101 and A\*3301.

**HXB2 Location** RT (158–166)**Author Location** RT**Epitope** AIFQSSMTK**Immunogen** HIV-1 infection**Species (MHC)** human (A11)**References** Wagner *et al.* 1998a

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1  $\alpha$  and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules.

**HXB2 Location** RT (158–166)**Author Location** RT (325–333 LAI)**Epitope** AIFQSSMTK**Subtype** B**Immunogen** peptide-HLA interaction**Species (MHC)** human (A11)**References** Menendez-Arias *et al.* 1998; Zhang *et al.* 1993

- Exploration of A11 binding motif, based on Nixon *et al.* 1991.

**HXB2 Location** RT (158–166)**Author Location** RT (325–333 LAI)**Epitope** AIFQSSMTK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A11)**Keywords** review**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.

**HXB2 Location** RT (158–166)**Author Location** Pol (305–313 93TH253 subtype CRF01)**Epitope** AIFQSSMTK**Epitope name** P313-321**Subtype** CRF01\_AE**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human (A11)**Keywords** HIV exposed persistently seronegative (HEPS)**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 128 who was HLA A11/A33.
- This epitope was strongly reactive in HIV+ study subjects 053 and 184 who carried HLA-A11.

**HXB2 Location** RT (158–166)**Author Location** Pol (305–313 93TH253 subtype CRF01)**Epitope** AIFQSSMTK**Subtype** CRF01\_AE**Immunogen** HIV-1 infection**Species (MHC)** human (A11)**Keywords** subtype comparisons**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined.

- 6/8 tested FSWs recognized this epitope.
- An HLA-A11 tetramer was made for this epitope, which was recognized by two subjects – and both subjects had expanded tetramer staining T-cell populations after *in vitro* stimulation.
- This epitope was highly conserved in other subtypes, and exact matches were common.

**HXB2 Location** RT (158–166)

**Author Location** RT (158–166 IIB)

**Epitope** AIFQSSMTK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** epitope processing, escape

**References** Moore *et al.* 2002b

- HIV polymorphisms in the RT protein were examined relation to HLA alleles found in a population of 473 participants in the Western Australian HIV Cohort Study. 64 significant associations between polymorphisms at particular positions and HLA alleles were detected, for HLA-B7, -B12, -B35 and -B15. Fifteen of these were in positions with known epitopes, 4 in anchor residues, 11 in other positions. Six additional polymorphic sites associated with particular HLA molecules flanked known epitopes and may relate to processing.
- HLA-A11+ individuals with a K166x (4/19) substitution had higher viral loads than those that did not, suggesting escape was associated with diminished immune control of viremia.

**HXB2 Location** RT (158–166)

**Author Location** Pol

**Epitope** SIFQSSMTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B60, B8, Bw6

**Keywords** HAART, ART

**References** Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful antiviral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2–4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

**HXB2 Location** RT (158–166)

**Author Location** Pol (314–322)

**Epitope** AIFQSSMTK

**Epitope name** AK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** optimal epitope

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For one of the escape variants, a novel CD8 T-cell response equal in magnitude to the wild type, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wild type.
- This epitope did not vary.

**HXB2 Location** RT (158–166)

**Author Location** Pol (314–322)

**Epitope** AIFQSSMTK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** RT (158–166)

**Author Location** Pol (313–321)

**Epitope** AIFQSSMTK

**Epitope name** AK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A\*01, A\*11, B\*08, B\*15, Cw\*04, Cw\*07

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** escape, optimal epitope

**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences *in vivo*. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The AK9 variant AIFQSSMT<sub>r</sub> was essentially the only form of the epitope detected over a 5-year period in this person. Elispot reactions indicated the T-cell clones only recognized the autologous form, not the B clade consensus, AIFQSSMTK. Two rare variants were observed at the 5-year time point, tIFQSSMT<sub>r</sub> and AIFQSSMar.

**HXB2 Location** RT (158–166)

**Author Location** RT

**Epitope** AIFQSSMTK  
**Epitope name** A11-AK9 (RT)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (158–166)  
**Author Location** Pol (325–333)  
**Epitope** AIFQSSMTK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301, A11, A33)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B  
**Keywords** Th1, characterizing CD8+ T cells  
**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of the patients responded to this peptide with GzB producing cells, while none of the patients responded with IFN-gamma producing cells.

**HXB2 Location** RT (158–166)  
**Author Location** RT (B consensus)  
**Epitope** AIFQSSMTK  
**Epitope name** ATK9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11, A3)  
**Donor MHC** A02, A11, B18, B44, Cw12, Cw5; A03, B14, B60, Cw3, Cw7; A01, A03, B08, B14, Cw7, Cw8  
**Country** United States  
**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** assay standardization/improvement, cross-presentation by different HLA, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 3/9 individuals recognized this epitope, two presented by HLA-A3, one presented by HLA-A11.

**HXB2 Location** RT (158–166)  
**Author Location** RT (325–333 IIIB)  
**Epitope** AIFQSSMTK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Keywords** responses in children, mother-to-infant transmission  
**References** Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- AIFQSSMTR and AILQSSMTK, naturally occurring variants, were found in infant, and are recognized.
- TISQSSMTK, a naturally occurring variant, was found in infant and is not recognized.

**HXB2 Location** RT (158–166)  
**Author Location** RT (325–333 LAI)  
**Epitope** AIFQSSMTK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Keywords** subtype comparisons  
**References** Cao *et al.* 1997a

- The consensus peptide of B and D clade viruses is AIFQSSMTK.
- The consensus peptide of a subset of As is AIFQASMTK and it is less able to stimulate the CTL clone.
- The consensus peptide of a subset of As is SIFQSSMTK and is as reactive as the originally defined epitope.

**HXB2 Location** RT (158–166)  
**Author Location** Pol (325–333 IIIB)  
**Epitope** AIFQSSMTK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Keywords** responses in children, mother-to-infant transmission, escape  
**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- One variant found in an infant gave a positive CTL response: AIFQSSMTR.
- AIFLSSMTK and TISQSSMTK were escape mutants.

**HXB2 Location** RT (158–166)

**Author Location** RT (325–333 SF2)

**Epitope** AIFQSSMTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 0/7 group 1, 0/4 group 2, and 1/2 group 3.

**HXB2 Location** RT (158–166)

**Author Location** RT (158–166)

**Epitope** AIFQSSMTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.
- In two of the subjects, AIFQSSMTK was the dominant epitope.

**HXB2 Location** RT (158–166)

**Author Location** RT Pol (313–321)

**Epitope** AIFQSSMTK

**Epitope name** A3-ATK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.

- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 3/7 individuals began to have detectable responses to this epitope after STI.

**HXB2 Location** RT (158–166)

**Author Location** RT (158–166)

**Epitope** AIFQSSMTK

**Epitope name** A3-AK9 Pol

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant aifqssmIk. The CTL response to the second variant was zero or low at all time-points. The CTL response to the first variant was also low, and declined over time.

**HXB2 Location** RT (158–166)

**Author Location** RT (158–166)

**Epitope** AIFQSSMTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** RT (158–166)

**Author Location** RT Pol (313–333)

**Epitope** AIFQSSMTK



- Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004
- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
  - 5/14 patients recognized this epitope.
- HXB2 Location** RT (158–166)  
**Author Location** Pol  
**Epitope** AIFQSSMTK  
**Epitope name** AK9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A1, A3, B57, B7, Cw6, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a
- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - One escape mutation, at position 9, aifqssmtI, was found not to correspond to the most polymorphic residues in the epitope.
- HXB2 Location** RT (158–166)  
**Author Location** RT  
**Epitope** AIFQSSMTK  
**Epitope name** A3-ATK9(RT)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
  - The most frequently recognized epitopes also elicited the greatest CTL response.
  - HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
  - HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (158–166)  
**Author Location** RT (325–333 LAI)  
**Epitope** AIFQSSMTK  
**Epitope name** P3  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3 supertype)  
**Keywords** HAART, ART, supertype  
**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** RT (158–166)  
**Author Location** Pol (337–345)  
**Epitope** AIFQSSMTK

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3 supertype)  
**Keywords** supertype, rate of progression  
**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** RT (158–166)  
**Author Location** Pol  
**Epitope** AIFQSSMTK  
**Epitope name** 1339

**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301, A\*6801, A11, A3, A33)  
**Donor MHC** A02, A03, B08, B51, Cw01, Cw07; A03, A26, B08, B52; A03, A11, B05, B14, Cw08  
**Country** United States  
**Assay type** T-cell Elispot

**Keywords** binding affinity, supertype, computational epitope prediction, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC superotypes.
- Estimated binding probability for AIFQSSMTK: 59% Supertype epitope binding to A03, A3.1, A11, A6801, A33.

**HXB2 Location** RT (158–166)

**Author Location** Pol (313–321)

**Epitope** AIFQSSMTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11, A3)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** RT (158–166)

**Author Location** Pol (325–333)

**Epitope** AIFQSSMTK

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (A11, A3, A33)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- Variants (S/A)IFQSSMTK are specific for the A/B clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A3 women, 2/2 HEPS and 3/3 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in one of the 2/2 HEPS cases and in one of the 3/3 HIV-1 infected women.

**HXB2 Location** RT (158–166)

**Author Location** Pol (325–333)

**Epitope** AIFQSSMTK

**Immunogen** peptide-HLA interaction

**Species (MHC)** (A11, A3, A33, A68)

**Assay type** HLA binding

**Keywords** binding affinity, immunodominance

**References** Racape *et al.* 2006

- Interaction between purified HLA-A3 molecules and several dominant CD8 epitopes was characterized. Amplitude, stability, and kinetic parameters of the interaction between HLA-A3, peptides, and anti-HLA mAbs were tested.

- Epitopes tested bound strongly to HLA-A3 and formed very stable complexes.

- Gag epitope RLRPGGKKK and Nef epitope RLAFHHVAR complexes with HLA-A3 were not recognized by the A11.1 mAb specific to HLA-A3 alleles. The proposed explanation was that Arg at position P1 of the peptide may push the  $\alpha$ 2 helix residue and affect mAb recognition.

**HXB2 Location** RT (158–166)

**Author Location** RT (325–333 LAI)

**Epitope** AIFQSSMTK

**Subtype** B

**Immunogen**

**Species (MHC)** human (A33)

**References** Rowland-Jones 1995

- Defined as minimal peptide by titration curve, S. Rowland-Jones, pers. comm.

**HXB2 Location** RT (158–166)

**Author Location**

**Epitope** AIFQSSMTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A33)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML1668.

**HXB2 Location** RT (158–182)

**Author Location** RT (325–349 PV22)

**Epitope** AIFQSSMTKILEPFRKQNPDIYIQ

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Jassoy *et al.* 1993

- HIV-1 specific CTLs release  $\gamma$ -IFN, and  $\alpha$ - and  $\beta$ -TNF.

**HXB2 Location** RT (158–182)

**Author Location** RT (325–349)

**Epitope** AIFQSSMTKILEPFRKQNPDIYIQ

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Price *et al.* 1995

- Study of cytokines released by HIV-1 specific activated CTL.

**HXB2 Location** RT (159–167)

**Author Location** RT Pol

- Epitope** IFQSSMTKI  
**Epitope name** P  
**Subtype** A, B, C  
**Immunogen** vaccine  
*Vector/Type:* DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT
- Species (MHC)** mouse (H-2K<sup>d</sup>)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism
- References** Larke *et al.* 2007
- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
  - After immunization with A-clade vaccine, index epitope P, IFQSSMTKI, and variant IFQaSMTKI were recognized. Variant IFQcSMTKI was not recognized.
- HXB2 Location** RT (159–167)  
**Author Location** RT (C-96BW15C05)  
**Epitope** IFQSSMTKI  
**Epitope name** E  
**Subtype** C  
**Immunogen** vaccine  
*Vector/Type:* DNA, alphavirus replicon  
*Strain:* C clade C-96BW04.09, C clade C-96BW15C05 *HIV component:* Gag, Gag-Pol, Pol
- Species (MHC)** mouse (H-2d)  
**Assay type** Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes, vaccine antigen design
- References** Megede *et al.* 2006
- HIV clade C gag, pol and fusion gagpol vaccines were compared in mice. Breadth of T cell responses was improved in mice immunized with gagpol fusion genes, compared to single antigen constructs. 5 new murine CD8+ T cell epitopes were mapped.
  - This is a novel epitope.
- HXB2 Location** RT (164–172)  
**Author Location** RT (1645–172)  
**Epitope** MTKILEPFR  
**Epitope name** MR9  
**Immunogen**  
**Species (MHC)** human (A\*0301)  
**References** Zimbwa *et al.* 2007

- E169D is a processing mutation for HLA-B\*0702 restricted SPAIFQSSM (SM9) as well as an epitope variation for HLA-A\*0301 restricted MTKILEPFR (MR9).
- CTL recognition of MR9 was detected 5 days post-infection with wild type (169E) HIV-1, but not with mutant 169D virus bearing epitope MTKILdPFR.
- Binding assays found a 44% reduction in binding to HLA-A\*0301 by the variant epitope MTKILdPFR.
- Mutation 169D lies within MR9. In vitro proteasome processing assays showed that both wild type or variant 27-mer synthetic peptide QGWKGGSPAIFQSSMTKILE(d)PFRKQNPd released appropriate MR9-intermediate peptides within 6 h.

**HXB2 Location** RT (164–172)

**Author Location** Pol (343–351)

**Epitope** MTKILEPFR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 4/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** RT (164–172)

**Author Location** Pol (319–327)

**Epitope** MTKILEPFR

**Subtype** B

**Immunogen** HIV-1 infection, peptide-HLA interaction

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** immunodominance

**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, MTKILEPFR, is similar to human protein Piwi-like 2, sequence MTKILEPc and human protein SON DNA Binding protein, sequence sMTKILdSF.

**HXB2 Location** RT (173–181)  
**Author Location** RT (173–181 LAI)  
**Epitope** KQNPDIIVY  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (A\*3002)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008; Goulder *et al.* 2001a  
 • C. Brander notes this is an A\*3002 epitope.

**HXB2 Location** RT (173–181)  
**Author Location** RT  
**Epitope** KQNPDIIVY  
**Epitope name** KY9 (RT-53)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3002)  
**References** Goulder *et al.* 2001a  
 • HLA-A\*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule.  
 • A rapid method was developed combining ELISPOT with intracellular IFN- $\gamma$  staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood.  
 • Two individuals were studied: Subject 199 (HLA A\*0201/\*3002 B\*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A\*3002/ B53/\*5801 Cw4/7) an African-Caribbean.  
 • In both HLA-A\*3002 individuals the response to RSLYNT-VATLY was dominant.  
 • In subject 199 four additional A\*3002 epitopes were identified.  
 • Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)

**HXB2 Location** RT (173–181)  
**Author Location** (C consensus)  
**Epitope** AQNPEIIVY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3002)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004  
 • HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.  
 • This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** RT (173–181)  
**Author Location**  
**Epitope** KQNPDIIVY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A30)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** supertype, cross-presentation by different HLA  
**References** Frahm *et al.* 2007

• 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.  
 • In addition to its known HLA association (A30), an additional HLA (A6801) was statistically predicted to be associated with this epitope.

**HXB2 Location** RT (173–181)  
**Author Location** RT  
**Epitope** KQNPDIIVY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, rate of progression, immunodominance  
**References** Frahm *et al.* 2006  
 • CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects in spite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.  
 • KQNPDIIVY of clade B is a potential HLA-B\*1503-restricted epitope, with epitope KQNPEIIVY found in clade C.

**HXB2 Location** RT (173–183)  
**Author Location** (C consensus)  
**Epitope** AQNPEIIVYQY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3002)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007  
 • A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- AQNPEIVYQY is an optimal epitope.

**HXB2 Location** RT (175–183)  
**Author Location** (C consensus)  
**Epitope** NPEIVYQY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*18)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the I4 residue of NPEIVYQY are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** RT (175–183)  
**Author Location** (C consensus)  
**Epitope** NPEIVYQY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*35)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- NPEIVYQY is an optimal epitope.

**HXB2 Location** RT (175–183)  
**Author Location** RT (328–336 IIIB)  
**Epitope** NPDIIVYQY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**References** Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- 3/7 B35-positive individuals had a CTL response to this epitope.
- D to E, or V to I, substitutions at positions 3 or 5, respectively, reduces CTL activity and binding to B\*3501.

**HXB2 Location** RT (175–183)  
**Author Location** RT (342–350 LAI)  
**Epitope** HPDIIVYQY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*3501 epitope. Variant NPDIIVYQY also noted.

**HXB2 Location** RT (175–183)  
**Author Location** Pol (330–338)  
**Epitope** NPDIIVYQY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**References** Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B\*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

**HXB2 Location** RT (175–183)  
**Author Location** RT (175–183 IIIB)  
**Epitope** NPDIIVYQY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**Keywords** epitope processing, escape  
**References** Moore *et al.* 2002b

- HIV polymorphisms in the RT protein were examined relation to HLA alleles found in a population of 473 participants in the Western Australian HIV Cohort Study. 64 significant associations between polymorphisms at particular positions and HLA alleles were detected, for HLA-B7, -B12, -B35 and -B15. Fifteen of these were in positions with known epitopes, 4 in anchor residues, 11 in other positions. Six additional polymorphic sites associated with particular HLA molecules flanked known epitopes and may relate to processing.
- NPDIIVYQY was one of two epitopes characterized in detail. D177x substitutions are known to specifically abrogate binding to HLA-B\*3501, and not other B\*35 subtypes. D177x substitutions were associated with people who carried HLA-B\*3501 and not other B\*35 subtypes; considering high resolution typing generally strengthened the B\*35 associations.

**HXB2 Location** RT (175–183)  
**Author Location** RT (175–183)  
**Epitope** NPDIIVYQY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**Donor MHC** A\*2301, B\*1503, B\*3501, Cw2, Cw7  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** binding affinity, acute/early infection, early-expressed proteins  
**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ INF- $\gamma$  T-cell responses in 21 men within 15-92days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of INF- $\gamma$

secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.

- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** RT (175–183)

**Author Location** Pol (330–338)

**Epitope** HPDIVIYQY

**Epitope name** HY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** escape, acute/early infection

**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this epitope was not detected until month 25.

**HXB2 Location** RT (175–183)

**Author Location**

**Epitope** NPEIVYIYQY

**Epitope name** NY9

**Immunogen**

**Species (MHC)** human (B18)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B18 epitope.

**HXB2 Location** RT (175–183)

**Author Location** RT (342–350 LAI)

**Epitope** HPDIVIYQY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** review

**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.

**HXB2 Location** RT (175–183)

**Author Location** RT (329–337)

**Epitope** HPDIVIYQY

**Subtype** B

**Immunogen** HIV-1 or HIV-2 infection

**Species (MHC)** human (B35)

**Country** Gambia

**Keywords** HIV exposed persistently seronegative (HEPS), HIV-2

**References** Rowland-Jones *et al.* 1995

- HIV-1 infected and HIV-2-infected B35+ subjects recognized both the HIV-1 (HPDIVIYQY) and HIV-2 forms (NPDVILIYQY). NPDIVIYQY preferred sequence for some CTL clones.

**HXB2 Location** RT (175–183)

**Author Location** (SF2)

**Epitope** NPDIVIYQY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** binding affinity, rate of progression, escape

**References** Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals – only one of these reduced the binding of the peptide to B35 and was shown to be an escape mutation.
- npEiviyqy was found in 8/10 of the B35+ individuals, and two of the B35- individuals—the D→E substituted peptide had reduced binding affinity to B35 and may be an escape mutant.

**HXB2 Location** RT (175–183)

**Author Location** RT (329–337)

**Epitope** HPDIVIYQY

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (B35)

**References** Lalvani *et al.* 1997

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers.
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors.

**HXB2 Location** RT (175–183)

**Author Location** RT (328–336 IIIB)

**Epitope** NPDIVIYQY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Menendez-Arias *et al.* 1998; Shiga *et al.* 1996

- Binds HLA-B\*3501.

- CTL activity to this epitope was originally detected in a long-term survivor, however it has since been found in normal progressors – it is cross-reactive with HIV-2 (HPDILYQY), but D3E and V5I substitutions reduce binding Menendez-Arias *et al.* [1998]

**HXB2 Location** RT (175–183)

**Author Location** RT (328–336 IIB)

**Epitope** NPDIVYQY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** review, escape

**References** Menendez-Arias *et al.* 1998; Sipsas *et al.* 1997

- HIV IIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIB.
- NPDIIIYQY, a variant found in HIV-1 JRCSF, was also recognized.
- NPEIVYQY, was also recognized.
- NPDLVIYQY, was also recognized.
- Menendez-Arias *et al.* [1998], in a review, notes that the YXDD motif, highly conserved among polymerases, overlaps this epitope – CTL activity to this epitope was originally detected in a long-term survivor, however it has since been found in normal progressors – it is cross-reactive with HIV-2 (HPDILYQY), but D3E and V5I substitutions reduce binding.

**HXB2 Location** RT (175–183)

**Author Location** RT

**Epitope** NPDIVYQY

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B35)

**Keywords** review, subtype comparisons, HIV exposed persistently seronegative (HEPS)

**References** Menendez-Arias *et al.* 1998; Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is HPDIVYQY.
- The D subtype consensus is NPEIVYQY.
- Menendez-Arias *et al.* [1998], in a review, notes that the YXDD motif, highly conserved among polymerases, overlaps this epitope – CTL activity to this epitope was originally detected in a long-term survivor, however it has since been found in normal progressors – it is cross-reactive with HIV-2 (HPDILYQY), but D3E and V5I substitutions reduce binding.

**HXB2 Location** RT (175–183)

**Author Location** Pol (subtype B)

**Epitope** NPDIVYQY

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B35)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- Clade A version of epitope HPDIVYQY, Clade D NPEIVYQY.

**HXB2 Location** RT (175–183)

**Author Location** Pol

**Epitope** HPDIVYQY

**Immunogen**

**Species (MHC)** human (B35)

**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 version of this epitope is not conserved: NPDVILIYQY, but the CTLs are cross-reactive – one of five B35 CTL epitopes that are cross-reactive, see also Rowland-Jones *et al.* [1995]

**HXB2 Location** RT (175–183)

**Author Location**

**Epitope** HPDIVYQY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** acute/early infection

**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWILGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** RT (175–183)  
**Author Location** Pol (subtype A)  
**Epitope** HPDIVIYQY  
**Subtype** A  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- HPDIVIYQY or NPDIVIYQY was recognized in 1 of the 6 women (ML857), and the response was present in the last available sample prior to seroconversion, 7 months.
- 20/20 sequences of the infecting strain had three substitutions in this epitope, all 20 were NpQiIiyqy, and this form was not recognized by CTL from ML 857 – this was the only case in the study where a virus carrying an unrecognized form of the epitope broke through.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- NPDIVIYQY was recognized by 1/22 HEPS control sex workers, ML887.

**HXB2 Location** RT (175–183)  
**Author Location** RT (175–183 SF2)  
**Epitope** NPDIVIYQY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 1/1 group 3.

**HXB2 Location** RT (175–183)  
**Author Location** Pol (342–350)  
**Epitope** HPDIVIYQY  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (B35)  
**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- Variants (H/N)PDIVIYQY are specific for the A/B clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B35 women, 2/3 HEPS and 1/4 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in only one of the 2/3 HEPS cases, and was not to this epitope in the one responsive HIV-1 infected women.
- Subject ML 857 shifted from a A\*6802 DTVLEDINL and B35 (H/N)PDIVIYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion and the loss of the pre-seroconversion response was not due to sequence variation within these epitopes.

**HXB2 Location** RT (175–183)

**Author Location**

**Epitope** HPDIVIYQY

**Epitope name** Pol-HY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 4/21 (19%) recognized this epitope.

**HXB2 Location** RT (175–183)

**Author Location** Pol

**Epitope** NPDIVIYQY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** A11, A3, B35, B51

**Keywords** mother-to-infant transmission

**References** Sabbaj *et al.* 2002

- IFN $\gamma$  T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested with using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- T-cells in breast milk from a volunteer who was HLA A3, A11, B35, B51 induced IFN $\gamma$  after stimulation with a peptide that carries known B35 epitope NPDIVIYQY.



- The frequencies of responses in the two compartments differed, and 2/4 women that responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

**HXB2 Location** RT (175–183)

**Author Location** Pol

**Epitope** HPDIVIYQY

**Subtype** A

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human, macaque (B35)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** RT (175–183)

**Author Location** Pol (342–350)

**Epitope** HPDIVIYQY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** Th1, characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN- $\gamma$  and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN- $\gamma$  only, and the other one (Tc1c) secretes GzB only.
- None of three patients responded to this peptide with GzB producing cells, while one of the patients responded with IFN- $\gamma$  producing cells.

**HXB2 Location** RT (175–183)

**Author Location** RT Pol (330–338)

**Epitope** HPDIVIYQY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/9 patients recognized this epitope.

**HXB2 Location** RT (175–183)

**Author Location** RT

**Epitope** NPDIVIYQY

**Epitope name** B35-NQY9(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (175–183)

**Author Location** RT

**Epitope** HPDIVIYQY

**Epitope name** B35-HY9(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
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- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (175–183)

**Author Location**

**Epitope** NPDIVYQY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope NPDIVYQY elicited a magnitude of response of 180 SFC with a functional avidity of 0.0005nM and binding affinity of 9nM.

**HXB2 Location** RT (175–183)

**Author Location** RT (329–337)

**Epitope** NPDVILIQY

**Subtype** HIV-2

**Immunogen** HIV-1 or HIV-2 infection

**Species (MHC)** human (B35)

**Country** Gambia

**Keywords** HIV exposed persistently seronegative (HEPS), HIV-2

**References** Rowland-Jones *et al.* 1995

- HIV-1 infected and HIV-2-infected B35+ subjects recognized both the HIV-1 (HPDIVYQY) and HIV-2 forms (NPDVILIQY). NPDIVYQY preferred sequence for some CTL clones.

**HXB2 Location** RT (175–184)

**Author Location** RT (175–184 LAI)

**Epitope** NPDIVYQYM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**References** Samri *et al.* 2000

- This epitope contains the mutation M184V, a frequent mutation induced by nucleoside reverse transcriptase inhibitors.
- Patient 246#1 (B51), was found by ELISPOT to recognize the wild type and the mutated peptide after zidovudine treatment.

- The resistance mutation M184V gave an increased predicted binding score to B51 ([http://bimas.dcrn.nih.gov/molbio/hla\\_bind](http://bimas.dcrn.nih.gov/molbio/hla_bind)) compared to the wildtype RT sequence and also an increased ELISPOT reactivity.

**HXB2 Location** RT (175–199)

**Author Location** RT (342–366 LAI)

**Epitope** NPDIVYQYMDLLVYVGSDEIGQHR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Menendez-Arias *et al.* 1998; Walker *et al.* 1989

- One of five epitopes defined for RT-specific CTL clones in this study.

**HXB2 Location** RT (179–187)

**Author Location** RT (179–187)

**Epitope** VIYQYMDLL

**Epitope name** VL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

**HXB2 Location** RT (179–187)

**Author Location** RT (179–187)

**Epitope** VIVQYMDLL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, VIVQYMDDL, was detected within overlapping peptide RKQNPDIVIVQYMDDLIV.

**HXB2 Location** RT (179–187)

**Author Location** RT

**Epitope** VIVQYMDDL

**Immunogen** vaccinia

*Vector/Type:* vaccinia

**Species (MHC)** human (A\*0201)

**References** Hanke *et al.* 1998a; Hanke *et al.* 1998b

- This epitope was shown to be processed and presented to appropriate CTL clones upon infection of human target cells with vaccinia virus Ankara (VVA) carrying 20 HIV-1 epitopes recognized by humans.

**HXB2 Location** RT (179–187)

**Author Location** RT

**Epitope** VIYQYMDDL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Tan *et al.* 1999

- Adoptive transfer of two autologous *in vitro*-expanded CTL clones against the A\*0201 restricted epitopes SLYNTVATL and VIYQYMDDL were infused into a patient – they were well tolerated, but the SLYNTVATL clone was shown by tetramer staining to be rapidly eliminated through apoptosis, and the treatment had no impact upon viral load and CD4 and CD8 cell counts.
- Tetramer staining failed for the VIYQYMDDL epitope as the tetramer was unstable.

**HXB2 Location** RT (179–187)

**Author Location** Pol (346–354)

**Epitope** VIYQYMDDL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** epitope processing, immunodominance, escape

**References** Sewell *et al.* 1999

- Proteasome regulation influences epitope processing and could influence patterns of immunodominance.
- The proteasome is inhibited by lactacystin treatment, and gamma IFN induces expression of proteasome subunits, LMP2 and LMP7, which combine with the proteasome to create an immunoproteasome.
- IFN-gamma induction of the immunoproteasome and lactacystin inhibition increases the presentation of the A\*0201 VIYQYMDDL epitope, but decreases the presentation of the A\*0201 ILKEPVHGV epitope, which is immunodominant

within pol proteins, showing the two epitopes are processed by different pathways.

- ILKEPVHGV seems to be processed by the classical proteasome pathway, while VIYQYMDDL appears to be destroyed by this pathway.

- This epitope contains the catalytic site (YMDD) of RT, a conserved sequence in HIV-1 which restricts escape mutants.

**HXB2 Location** RT (179–187)

**Author Location** RT (346–354 LAI)

**Epitope** VIYQYMDDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** review

**References** Harrer *et al.* 1996a; Menendez-Arias *et al.* 1998

- The substitution VIYQYVDDL abrogates CTL response and confers drug resistance.
- Menendez-Arias *et al.* [1998], in a review, notes that this epitope includes catalytic residues (Asp-185 and Asp-186) in the active site of RT.

**HXB2 Location** RT (179–187)

**Author Location** RT (346–354 LAI)

**Epitope** VIYQYMDDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0201 epitope.

**HXB2 Location** RT (179–187)

**Author Location** RT (346–354)

**Epitope** VIYQYMDDL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** review, escape

**References** Brander *et al.* 1998a; Menendez-Arias *et al.* 1998

- Of 17 infected HLA A\*0201 subjects, 13 had CTL responses against the p17 SLYNTVATL epitope, six recognized ILKEPVHGV and five recognized VIYQYMDDL, and there was no correlation between viral load and recognition of a specific epitope or evidence of immune escape.
- Only one subject had CTL against all three epitopes.
- Subjects were part of the San Francisco City Clinic Cohort, the ARIEL project and from the Boston area.
- In the review Menendez-Arias *et al.* [1998] the authors note that substitution of three residues in this epitope can confer resistance to RT inhibitors (1, 3, and 6) – substitutions V1E and M6V abolish CTL activity, and M6V confers resistance to 3TC – substitution Y3C reduces CTL activity and is associated with resistance to non-nucleoside RT inhibitors.

**HXB2 Location** RT (179–187)

**Author Location** RT

**Epitope** VIYQYMDDL

**Epitope name** RT VL9

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)

**Keywords** subtype comparisons, supertype, computational epitope prediction

**References** Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, including RT VL9, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- RT VL9 was not recognized by any of the 22 HLA-A2 patients with chronic HIV-1 infection or the 13 HLA-A2 patients with acute HIV-1 infection included in this study.

**HXB2 Location** RT (179–187)

**Author Location** RT (346–354)

**Epitope** VIYQYMDDL

**Epitope name** VL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Dela Cruz *et al.* 2000

- Integration of HIV RT CTL epitopes into the N-terminus of the HLA-A2 heavy chain, or tethering the epitopes to the target chain, resulted in epitope-specific lysis by CD8+ CTL.
- These antigens could also be used to stimulate primary responses *in vitro*.

**HXB2 Location** RT (179–187)

**Author Location** Pol (346–354)

**Epitope** VIYQYMDDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** epitope processing, immunodominance

**References** Sewell *et al.* 2002

- Epitope processing of three different HLA-A\*0201 HIV epitopes was shown to use different pathways, which might influence patterns of immunodominance. .174 cells were used that lack TAP1 and TAP2 genes, as well as the LMP2 and LMP7 genes that encode the beta-subunits of the immunoproteasome. These genes could be added back through transfection to study processing.
- ILKEPVHGV was efficiently presented in TAP-1 and -2 transfected cells while VIYQYMDDL and SLYNTVATL were not. VIYQYMDDL was destroyed by the MB1 subunit of the protease, and could be expressed in the presence of the protease inhibitor lactacystin, but SLYNTVATL expression was not restored. SLYNTVATL expression was unaltered by lactacystin in a wild type cell line.

**HXB2 Location** RT (179–187)

**Author Location** RT (346–354 LAI)

**Epitope** VIYQYMDDL

**Epitope name** LR26

**Subtype** B

**Immunogen** vaccine

**Vector/Type:** peptide **Strain:** B clade LAI

**Adjuvant:** Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG

**Species (MHC)** mouse (A\*0201)

**Keywords** binding affinity, vaccine-specific epitope characteristics, immunodominance

**References** Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRAVFTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a strong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

**HXB2 Location** RT (179–187)

**Author Location** RT (346–354 LAI)

**Epitope** VIYQYMDDL

**Epitope name** LR26

**Subtype** B

**Immunogen** vaccine

**Vector/Type:** peptide **Strain:** B clade LAI

**Adjuvant:** Incomplete Freund's Adjuvant (IFA), IL-12, P30

**Species (MHC)** mouse (A\*0201)

**Keywords** vaccine-specific epitope characteristics, immunodominance

**References** Peter *et al.* 2002

- When HIV-1 peptides were used to vaccinate HLA-A2.1 transgenic A2-Kb mice, strong responses to five peptides were observed when the peptides were given individually, but immunodominance limited the response to some of the peptides when they were given in combination Peter *et al.* [2001]. IL-12 can counteract immunodominance in BALB/c mice, so it was given with the multiple epitope vaccination, and was instead found to specifically eliminate the HLA-A2.1-epitope CTL responses, but not Kb CTL responses. This was possibly a consequence of transient depletion of T-cells, B cells and macrophages in the spleen.

**HXB2 Location** RT (179–187)

**Author Location** Pol

**Epitope** VIYQYMDDL

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, vaccine

**Vector/Type:** DNA prime with modified vaccinia Ankara (MVA) boost **Strain:** A clade  
**HIV component:** p17 Gag, p24 Gag

**Species (MHC)** human, macaque (A\*0201)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  ELISPOT assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** RT (179–187)

**Author Location** RT (179–187)

**Epitope** VIYQYMDDL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* RT  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12

**Species (MHC)** mouse (A\*0201)

**Donor MHC** A2.1

**Assay type** Cytokine production, Chromium-release assay

**Keywords** binding affinity, vaccine-induced epitopes

**References** Okazaki *et al.* 2003

- Alanine substitutions of VIYQYMDDL were tested for importance of each amino acid for HLA-A2.1 binding. Peptide variant (vLyqymddV) showed an 8 fold higher MHC binding affinity than wild type. YLyqymddV had an even higher binding affinity, but the Y at position one blocked TCR recognition. The higher affinity form of vLyqymddV induced CTL *in vivo* that could protect against a vaccinia virus expressing RT and the wild type epitope.

**HXB2 Location** RT (179–187)

**Author Location** RT (179–187 MN)

**Epitope** VIYQYMDDL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** humanized mouse (A\*0201)

**Assay type** CD8 T-cell ELISPOT - IFN $\gamma$

**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy

**References** Isagulians *et al.* 2004

- Immunization of HLA-A\*0201-transgenic mice with synthetic genes encoding clusters of human A\*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains.
- This was one of five HLA-A\*0201 epitopes from the RT or protease proteins that was included in the polyepitope vaccine. When the transgenic HLA A\*0202 mice were vaccinated with the polyepitope construct or with a mixture of RT peptides, a sustained low level CD8+ T-cell gamma IFN response was observed, in contrast to when an intact RT gene was used for vaccination.

**HXB2 Location** RT (179–187)

**Author Location** Pol (346–354)

**Epitope** VIYQYMDDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** United States

**Assay type** CD8 T-cell ELISPOT - IFN $\gamma$ , CD8 T-cell ELISPOT granzyme B

**Keywords** Th1, characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of seven patients responded to this peptide with GzB producing cells, while none of the patients responded with IFN-gamma producing cells.

**HXB2 Location** RT (179–187)

**Author Location** (C consensus)

**Epitope** VIYQYMDDL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** South Africa

**Assay type** CD8 T-cell ELISPOT - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- VIYQYMDDL is an optimal epitope.

**HXB2 Location** RT (179–187)

**Author Location** RT (179–187)

**Epitope** VIYQYMDDL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, VIYQYMDDL, was predicted to be restricted by HLA A\*0201, A\*0205, A\*0207, A\*0214.

**HXB2 Location** RT (179–187)

**Author Location** Pol

**Epitope** VIYQYMDDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A\*02/A\*0201 restricted epitope, VIYQYMDDL was mutated to cIYQYMDDL in the daughter D2 isolate.

**HXB2 Location** RT (179–187)

**Author Location** RT

**Epitope** VIYQYMDDL

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A2)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A and D consensus sequences are both VIYQYMDDL.

**HXB2 Location** RT (179–187)

**Author Location** Pol (346–354)

**Epitope** VIYQYMDDL

**Immunogen** vaccine

*VectorType:* DNA prime with vaccinia boost

**Species (MHC)** human (A2)

**References** Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D<sup>d</sup> – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFD-SRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- VIYQYMDDL was recognized by 3 of the HLA-A2 patients.

**HXB2 Location** RT (179–187)

**Author Location** RT (179–187)

**Epitope** VIYQYMDDL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** escape, immunotherapy

**References** Schmitt *et al.* 2000

- The mutation M184V confers resistance to lamivudine, and is in the middle of the HLA-A2 epitope VIYQYMDDL.
- 1/28 individuals tested produced HIV-1 RT-specific CTL that recognized the peptide representing the lamivudine escape mutants VIYQYVDDL and VIYQYIDDL, but failed to recognize the wildtype epitope VIYQYMDDL.

- This suggests immunotherapy stimulating anti-VIYQYVDDL responses maybe helpful for reducing lamivudine escape.

**HXB2 Location** RT (179–187)

**Author Location** RT (179–187)

**Epitope** VIYQYMDDL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)

**HXB2 Location** RT (179–187)

**Author Location** Pol (339–347 93TH253 subtype CRF01)

**Epitope** VIYQYMDDL

**Epitope name** P334-342

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2.

**HXB2 Location** RT (179–187)

**Author Location** Pol (339–347 93TH253 subtype CRF01)

**Epitope** VIYQYMDDL

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 2/4 tested FSWs recognized the E clade version of this epitope, which is identical to the previously defined B clade version VIYQYMDDL.
- This epitope was conserved in many subtypes, and exact matches were very uncommon.

**HXB2 Location** RT (179–187)

**Author Location** RT (179–187)

**Epitope** VIYQYMDDL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)

- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

**HXB2 Location** RT (179–187)

**Author Location** Pol (346–354 LAI)

**Epitope** VIYQYMDDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART, epitope processing

**References** Kelleher *et al.* 2001a

- Ritonavir (RTV) inhibits chymotryptic activity in the 20S proteasome *in vitro*, as does Saquinavir (SQV) to a lesser extent; Indinavir (IDV) does not. Thus there is concern protease inhibitors may adversely effect CTL epitope processing, but this paper indicates that processing is not inhibited at therapeutically relevant concentrations of RTV when the proteasome is functioning in an intracellular context.
- RTV did not alter the presentation two RT A2 epitopes processed by distinct pathways: ILKEPVHGV, generated by the constitutive proteasome containing the MB1 beta subunit, and VIYQYMDDL which is dependent on IFN $\gamma$  induction of LMP7 which replaces MB1 in the immunoproteasome, and is destroyed by MB1 in the constitutive proteasome.
- RTV did not inhibit the processing and assembly of HLA-B35 or -A2, which are assembled with a rapid and moderate time course, respectively, or of HLA-A3, -B27 and -B39.

**HXB2 Location** RT (179–187)

**Author Location** Pol (334–)

**Epitope** VIYQYMDDL

**Epitope name** Pol334

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- 1/17 HIV-infected HLA-A2+ people in this study recognized this epitope.

**HXB2 Location** RT (179–187)

**Author Location** Pol (334–342)

**Epitope** VIYQYMDL**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Donor MHC** A02, B35, Bw62**Assay type** proliferation, Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** HAART, ART, memory cells, immune dysfunction**References** Gamberg *et al.* 2004a

- HAART restores HIV specific immunity after advanced infection by increase of CD4+ and CD8+ T cell numbers after suppression of viral replication. However, HIV specific CTLs emerged only with detectable viral replication breakthroughs and were short-lived while CD4+ T-cell responses remained compromised, suggesting failure of generating stable CD8+ memory T-cells in the absence of HIV-specific T-helper responses.

**HXB2 Location** RT (179–187)**Author Location** RT (179–187)**Epitope** VIYQYMDL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** Canada**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization**References** Mason *et al.* 2004

- Accumulation of specific antiretroviral drug-resistance mutations in Pol gene was shown to sustain and even enhance the antigenicity and immunogenicity of HIV-1 CTL epitopes in this region. Several different patterns of cross-reactivity and selective recognition of wild-type and variant epitopes were found.
- V1cQYMDL, VIYQYvDDL and V1cQYvDDL variants are detected due to appearance of Y181C and M184V resistance mutations. The double mutant was the only form recognized in one A02 treated individual, the epitope was not recognized in another.

**HXB2 Location** RT (179–187)**Author Location** RT Pol (334–342)**Epitope** VIYQYMDL**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** Spain**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/19 patients recognized this epitope.

**HXB2 Location** RT (179–187)**Author Location** Pol**Epitope** VIYQYMDL**Immunogen** HIV-1 exposed seronegative**Species (MHC)** human (A2)**Donor MHC** A\*02, A\*30, B\*15, B\*4402**Assay type** Tetramer binding, T-cell Elispot**Keywords** HIV exposed persistently seronegative (HEPS)**References** Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 4/8 HIV epitopes tested in an IFN $\gamma$  Elispot assay or tetramer assay. Responses were detected 8 and 28 weeks after exposure. No response to this epitope was detected by IFN $\gamma$  Elispot, but a response was detected by tetramer staining.

**HXB2 Location** RT (179–187)**Author Location** RT (179–187)**Epitope** VIYQYMDL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding**Keywords** acute/early infection, optimal epitope**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized in chronic infection.

**HXB2 Location** RT (179–187)**Author Location** RT (179–187 HXB2)**Epitope** VIYQYMDL**Epitope name** 51F**Subtype** B**Immunogen** vaccine*Vector/Type:* DNA *Strain:* multiple epitope immunogen *HIV component:* p17/p24 Gag, Pol *Adjuvant:* IL-12**Species (MHC)** transgenic mouse (A2)**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** vaccine-specific epitope characteristics, vaccine antigen design**References** Bolesta *et al.* 2005

- Immunization of transgenic mice with a codon-optimized hGagp17p24-Polp51 DNA plasmid, consisting of clusters of highly conserved CTL epitopes presented by multiple MHC class I alleles, induced 2- to 5-fold higher CD8+ T-cell responses than the corresponding full-length proteins. The



modified proteins had the ribosomal frameshift deleted, as well as the potentially immunosuppressive p15, and protease and integrase. This correlated with higher protection against challenge with Gag and Pol expressing recombinant vaccinia virus. Mice immunized with the hGagp17p24-Polp51 also showed an elevated level of type 1 cytokine production as well as an increased titer of p24- and RT-specific IgG2 antibody responses.

- This was 1 of 4 A2 gag/pol epitopes tested. Transgenic mice immunized with the deleted construct induced more potent EliSpot reactions to this epitope than those immunized with full length Gag/Pol.

**HXB2 Location** RT (179–187)

**Author Location** RT (346–354)

**Epitope** VIYQYMDL

**Epitope name** VL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** HAART, ART, optimal epitope

**References** Schmitt-Haendle *et al.* 2005

- CTL responses to 3 HLA-A2-restricted epitopes were investigated in 51 HIV-1 infected HLA-A2+ individuals. The most prevalent response was seen for IV9, followed by SL9. The VL9 epitope was not recognized.

**HXB2 Location** RT (179–187)

**Author Location** Pol (subtype B)

**Epitope** VIYQYMDL

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A\*0202, A2)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B and D clade viruses.

**HXB2 Location** RT (180–189)

**Author Location** RT (LAI)

**Epitope** IYQYMDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Recognized by CTL from a progressor, spans important RT functional domain.
- A previous study determined that this was an epitope recognized by a long-term survivor.

**HXB2 Location** RT (181–189)

**Author Location** RT (181–189)

**Epitope** YQYMDDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- Two patients developed responses to epitope YQYMDDL during primary infection and in early chronic infection.

**HXB2 Location** RT (181–189)

**Author Location** RT (181–189 LAI)

**Epitope** YQYMDDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity, computational epitope prediction

**References** Samri *et al.* 2000

- This epitope contains the mutation M184V, a frequent mutation induced by nucleoside reverse transcriptase inhibitors.
- High levels of recognition by ELISPOT were observed for zidovudine induced mutation YQYVDDL and for the wildtype peptide YQYMDDL in patient 250#0 (HLA-A\*0201), but neither were recognized by patient 201#5 (also HLA-A\*0201)
- Both the wild-type and the mutated peptide were computer predicted to have a high binding affinity for A2 ([http://bimas.dcrn.nih.gov/molbio/hla\\_bind](http://bimas.dcrn.nih.gov/molbio/hla_bind))

**HXB2 Location** RT (181–189)

**Author Location** RT (181–189)

**Epitope** YQYMDDL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, YQYMDDLYV, was predicted to be restricted by HLA A\*0201.

**HXB2 Location** RT (192–201)

**Author Location** RT (192–201)

**Epitope** DLEIGQHRTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

**HXB2 Location** RT (192–201)

**Author Location** Pol (192–201)

**Epitope** DLEIGQHRTK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. The dleMgqhrtk variant arose at late time points.

**HXB2 Location** RT (192–216)

**Author Location** RT (359–383 HXB2)

**Epitope** DLEIGQHRTKIEELRQHLLRWGLTT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**References** Menendez-Arias *et al.* 1998; Walker *et al.* 1989

- One of five epitopes defined for RT-specific CTL clones in this study.

**HXB2 Location** RT (192–216)

**Author Location** RT (191–215)

**Epitope** DLEIGQHRTKIEELRQHLLRWGFTT

**Immunogen** HIV-1 infection

**Species (MHC)** human (polyclonal)

**Keywords** HAART, ART, escape

**References** Haas *et al.* 1997; Menendez-Arias *et al.* 1998

- Polyclonal CTL recognition switched from RT 191-215 to RT 514-524 when AZT therapy selected for the resistance mutation, and presumably the escape variant, RT T215Y.

**HXB2 Location** RT (198–212)

**Author Location** RT (SF2)

**Epitope** HRTKIEELRQHLLRW

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

**HXB2 Location** RT (201–209)

**Author Location** RT (201–209)

**Epitope** KIEELRQHL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

**HXB2 Location** RT (201–210)

**Author Location** Pol

**Epitope** KIEELRQHLL

**Immunogen**

**Species (MHC)** human (B58)

**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFN $\gamma$  production in an ELISPOT assay.
- KIEELRQHLL was newly identified as a HLA-B58 epitope in this study, it had been previously shown to be presented by HLA-A2 and Bw60.
- KIEELRQHLL did not bind detectably to B7.

**HXB2 Location** RT (201–219)

**Author Location** RT

- Epitope** KIEELRQHLLRWGFTTPDK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004
- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
  - Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
  - In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
  - This overlapping peptide, KIEELRQHLLRWGFTTPDK, was differentially targeted across ethnic groups and had an overall frequency of recognition of 13.3% - 5.1% AA, 23.1% C, 25% H, 0% WI (P value = 0.0018).

- HXB2 Location** RT (202–210)  
**Author Location** RT (202–210 LAI)  
**Epitope** IEELRQHLL  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (B\*4001)  
**Keywords** optimal epitope  
**References** Altfeld *et al.* 2000; Frahm *et al.* 2008
- C. Brander notes this is a B\*4001 epitope.

- HXB2 Location** RT (202–210)  
**Author Location** Pol (357–365)  
**Epitope** IEELRQHLL  
**Epitope name** IL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4001)  
**Donor MHC** A\*0201, A\*2402, B\*4001, B\*5001, Cw03, Cw04

- Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization  
**References** Draenert *et al.* 2006
- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their sero-conversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
  - This epitope, IEELRQHLL (IL9) restricted by HLA-B\*4001, was one of two immunodominant responses. Variants that arose were vEELReHLL and IEELReHLL.

- HXB2 Location** RT (202–210)  
**Author Location** RT  
**Epitope** IEELRQHLL  
**Epitope name** B40-IL9(RT)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B40)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
  - The most frequently recognised epitopes also elicited the greatest CTL response.
  - HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
  - HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
  - In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

- HXB2 Location** RT (202–210)  
**Author Location** Pol  
**Epitope** IEELRQHLL  
**Epitope name** IL-9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B40)  
**Assay type** Other  
**Keywords** escape, TCR usage, immune evasion  
**References** Yu *et al.* 2007b

- The dependence of TCR clonotype recruitment on genetic background was determined by studying monozygotic twins infected with the same HIV-1 strain. After an early, initial correlation in the magnitude, specificity and immunodominance

of CTL response [Draenert et al. *J. Exp. Med.* 203:529-539(2006)], subsequent disease was mixed with respect to CTL epitopes' mutational escape. TCR alpha and beta chain repertoires were analyzed and it was found that their clonotypes in HIV-specific CTLs were broadly heterogeneous for both concordant and discordant epitope sequence evolution between the twins. Therefore initial TCR recruitment appears to be an entirely random process independent of genetic background of the infected individual.

- This epitope, IL9, showed concordant epitope evolution between the twins, but both alpha and beta TCR chains recruited were entirely different between them.

**HXB2 Location** RT (202–210)

**Author Location**

**Epitope** IEELRQHLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B40)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B40), an additional HLA (B37) was statistically predicted to be associated with this epitope.

**HXB2 Location** RT (202–210)

**Author Location** RT (SF2)

**Epitope** IEELRQHLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B60+ individuals that had a CTL response to this epitope broken down by group: 0/2 group 1, 1/1 group 2, and 0/0 group 3.

**HXB2 Location** RT (202–210)

**Author Location** RT (SF2)

**Epitope** IEELRQHLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes.
- B60 is present in 10-20% of the Caucasoid and very common in Asian populations.

**HXB2 Location** RT (202–210)

**Author Location** RT

**Epitope** IEELRQHLL

**Epitope name** IL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Donor MHC** A2, A24, B38, B60, Cw12, Cw2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HAART, ART, supervised treatment interruptions (STI), early treatment

**References** Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

**HXB2 Location** RT (202–210)

**Author Location** RT (202–210)

**Epitope** IEELRQHLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60, B61)

**Keywords** immunodominance

**References** Day *et al.* 2001

- No immunodominant responses were detected to five B61-restricted epitopes tested.
- All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response.

**HXB2 Location** RT (203–211)

**Author Location** RT

**Epitope** EELRQHLLR

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Donor MHC** A\*3101, A68, B\*4403, B51

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Arnedo-Valero *et al.* 2004

- T cell immune responses following STI were monitored in two chronically HIV-1 infected partners (A and B) who had contracted HIV-1 during 1992. Both were heterozygous for the CCR5 delta32, and had different HLAs and treatment histories. STI induced strong transitory CD4+ and CD8+ T cell responses in both patients. Patient A displayed broad

CD8+ T cell responses directed against Env, Pol, Gag, and Nef HIV-1 antigens. CTL responses in patient B were mainly directed against two epitopes: Gag(p24)NANPDSKTI and Pol(RT)EELRQHLLRW.

- Despite the host differences, both patients had similar dynamics of viral evolution and CD4+ T-cells, suggesting that good immune responses to STI may be more related to the virus than host characteristics in these cases.

**HXB2 Location** RT (203–212)

**Author Location** RT (LAI)

**Epitope** EELRQHLLRW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**References** Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- The only epitope recognized by CTL from a long-term survivor in two samples taken six years apart.
- Recognized by CTL from a progressor, EILKEPVGHG and TWETWWTEYW were also recognized.

**HXB2 Location** RT (203–212)

**Author Location** RT (203–212)

**Epitope** EELRQHLLRW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Country** Canada

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** HAART, ART, immunotherapy, variant cross-recognition or cross-neutralization

**References** Mason *et al.* 2004

- Accumulation of specific antiretroviral drug-resistance mutations in Pol gene was shown to sustain and even enhance the antigenicity and immunogenicity of HIV-1 CTL epitopes in this region. Several different patterns of cross-reactivity and selective recognition of wild-type and variant epitopes were found.
- EELRQHLwRW variant is detected due to appearance of L210W resistance mutation. The in this case, the wild-type epitope was preferentially recognized relative to the L210W variant.

**HXB2 Location** RT (203–212)

**Author Location** RT Pol (358–367)

**Epitope** EELRQHLLRW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.

- 9/11 patients recognized this epitope; of three B\*44 epitopes tested, this was the only one that was recognized by more than 2/11 patients.

**HXB2 Location** RT (203–212)

**Author Location** RT

**Epitope** EELRQHLLRW

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B44)

**Donor MHC** A01, A03, B39, B44, Cw4, Cw6

**Assay type** T-cell Elispot

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.

- This patient responded to 3/11 HIV epitopes tested in an IFN $\gamma$  EliSpot assay. Responses were detected 16 and 20 weeks after exposure, but were lost by week 80.

**HXB2 Location** RT (203–212)

**Author Location** p24

**Epitope** EELRQHLLRW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Donor MHC** A01, A32, B\*1410, B15; A\*3101, A68, B\*4403, B51

**Country** Spain

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Arnedo-Valero *et al.* 2004

- T cell immune responses following STI were monitored in two chronically HIV-1 infected partners (A and B) who had contracted HIV-1 during 1992. STI induced strong transitory CD4+ and CD8+ T cell responses in both patients. The viruses remained very closely related over 10 years, despite the two individuals having different HLA types; the authors suggest the maintained similarity does not support a strong role for HLA driven HIV diversity as has been claimed in Moore *et al.* (Science 2002).

- During the second treatment stop, patient A developed a strong proliferative response to p24, and multiple strong CD8+ T cell responses to Env, Pol, Gag and Nef. This patient was able to control viral load for two years follow up without therapy. Patient B developed a very weak CD4+ T cell response against p24 during breaks in therapy, and had CD8+ responses

to two epitopes. Patient A: A01, A32, B\*1410, B15; Patient B: A\*3101, A68, B\*4403, B51.

**HXB2 Location** RT (203–212)

**Author Location** RT (203–212)

**Epitope** EELRQHLLRW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Country** Canada

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** mimics

**References** Mason *et al.* 2005

- CTL responses against the IP-30 signal peptide associated with autoimmunity were shown to be elicited by stimulation of PBMCs from HIV-1 infected individuals with HIV protease peptide 76-84. In vitro stimulation with HIV PR 76-84 or the IP-30 signal peptide was shown to activate a comparable population of cross-reactive effector cells. None of the peptides activated CTL in non-HIV-infected individuals. IP-30 signal peptide was shown to have lower avidity T-cell interactions than the HIV peptide.
- As a control, responses to A2-restricted HIV epitopes ALVEICTEM, EELRQHLLRW, and LSPRTLNAW were shown not to give IP-30 responses.

**HXB2 Location** RT (204–212)

**Author Location** RT (204–212 HXB2)

**Epitope** ELRQHLLRW

**Epitope name** EW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2501)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Position 8 in the epitope had potentially experienced positive selection. ELRQHLLkW escape variant was found.

**HXB2 Location** RT (206–214)

**Author Location** RT Pol

**Epitope** RAHLLSWGf

**Epitope name** RT1

**Subtype** A, B, C

**Immunogen** vaccine

**Vector/Type:** DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost **Strain:** A clade, B clade, C clade Du422, Other **HIV component:** Gag, Nef, RT

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism

**References** Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
- After immunization with Clade A vaccine containing RT1, RAHLLSWGf, this index epitope was not recognized. Clade B vaccine containing RQHLLRWGL generated T cells that recognized its index epitope as well as variants RaHLLSWGf (Clade A index), RkHLLkWGf (Clade C index), RaHLLRWGf, RQHLLRWGf, ReHLLkWGf, ReHLLRWGf, RgHLLkWGf, RkHLLSWGf at lower levels. C Clade vaccine with index epitope RKHLLKWGF resulted in T cells that recognized that epitope, and Clade B index epitope RqHLLrWGL, and epitope RKHLLsWGf at 53%.

**HXB2 Location** RT (209–220)

**Author Location** RT (209–220)

**Epitope** LLRWGLTTPDKK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

**HXB2 Location** RT (209–220)  
**Author Location** RT (209–220 MN)  
**Epitope** LLRWGLTTPDKK  
**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** humanized mouse (A\*0201)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy

**References** Isagulians *et al.* 2004

- Immunization of HLA-A\*0201-transgenic mice with synthetic genes encoding clusters of human A\*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains.
- This was one of five HLA-A\*0201 epitopes from the RT or protease proteins that was included in the polyepitope vaccine. When the transgenic HLA A\*0202 mice were vaccinated with the polyepitope construct or with a mixture of RT peptides, a sustained low level CD8+ T-cell gamma IFN response was observed, in contrast to when an intact RT gene was used for vaccination.

**HXB2 Location** RT (209–220)  
**Author Location** RT (209–220)  
**Epitope** LLRWGLTTPDKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

**HXB2 Location** RT (210–220)  
**Author Location** Pol (209–220)  
**Epitope** LRWGFCTPDKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A2, B44, B57; A2, A29, B57, B62

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** HAART, ART, cross-presentation by different HLA, characterizing CD8+ T cells

**References** Mason & Grant 2005

- The common form of this epitope, LRWGFCTPDKK is weakly recognized in the context of HLA-A2, and it encompasses several common antiretroviral escape mutations. Responses were tested in 2 siblings.

- T215Y then Y215C antiretroviral therapy-associated mutations within the epitope induced a strong reaction, but changed the restriction of the epitope to HLA-B57. This mutation is thus suggested to potentially enhance CD8 T-cell recognition of HIV.

**HXB2 Location** RT (214–223)  
**Author Location** Pol  
**Epitope** FTTPDKKHQK

**Epitope name** 1267

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11, A68)

**Donor MHC** A11, A68, B42, B45, Cw16, Cw17

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, supertype, computational epitope prediction, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC superotypes.
- Estimated binding probability for FTTPDKKHQK:36% Supertype epitope binding to A68 and A11.

**HXB2 Location** RT (215–224)  
**Author Location** Pol  
**Epitope** TTPDKKHQKE

**Epitope name** 1281

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A68, B42, B45, Cw16, Cw17; A01, A68, B15, B40, Cw03

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, supertype, computational epitope prediction, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC superotypes.
- Estimated binding probability for TTPDKKHQKE:60% Supertype epitope binding to A68.

**HXB2 Location** RT (218–235)  
**Author Location** (C consensus)  
**Epitope** DKKHQKEPFLWMGYELH  
**Subtype** C  
**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1510)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (240–257)  
**Author Location** (C consensus)  
**Epitope** TVQPIQLPEKDSWTVNDI  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5301)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (240–257)  
**Author Location** RT (240–257 HXB2)  
**Epitope** TVQPIVLPEKDSWTVNDI  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** T-cell Elispot  
**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment  
**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** RT (243–252)

**Author Location** RT (LAI)  
**Epitope** PIVLPEKDSW  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5701)

- References** Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997
- Recognized by CTL from a progressor and a long-term survivor, KITTESIVIW was also recognized.

**HXB2 Location** RT (243–252)  
**Author Location** RT (LAI)  
**Epitope** PIVLPEKDSW  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5701)  
**Keywords** binding affinity, escape  
**References** Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Recognized by CTL from long-term survivor, whose CTL response persisted for more than 10 years – the substitution V3M reduced affinity but was well recognized, on the other hand V3T and D8G did not reduce affinity, but abrogated CTL response.

**HXB2 Location** RT (243–252)  
**Author Location** RT (410–419)  
**Epitope** PIVLPEKDSW

**Epitope name** PIV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Keywords** HAART, ART, acute/early infection  
**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B57+

**HXB2 Location** RT (243–252)  
**Author Location** RT  
**Epitope** PIVLPEKDSW  
**Epitope name** PIV

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Keywords** HAART, ART, supervised treatment interruptions (STI)  
**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.



**HXB2 Location** RT (243–252)  
**Author Location** RT Pol (398–407)  
**Epitope** PIVLPEKDSW

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)

**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ ,  
 Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment inter-  
 ruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 6/7 patients recognized this epitope.

**HXB2 Location** RT (244–252)

**Author Location**

**Epitope** IVLPEKDSW

**Epitope name** IW9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B\*57-restricted optimal epitope IVLPEKDSW was tested for immune response.
- No loss of recognition was seen for variants I147L (IVLPEKDSW) and I147M (mVLPEKDSW) in several subjects, none of whom had the I147M mutation.
- I146P variant, iVLPEKDSW, blocks presentation of epitope IW9.

**HXB2 Location** RT (244–252)

**Author Location** RT (244–252)

**Epitope** IVLPEKDSW

**Epitope name** rtIW9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Country** United Kingdom, Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** TCR usage, structure, characterizing CD8+ T cells

**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIMPF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.

- In addition, immunodominancy of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFN-PEVIMPF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** RT (244–252)

**Author Location** RT (399–407)

**Epitope** IVLPEKDSW

**Immunogen**

**Species (MHC)** human (B\*5701)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- Subtype of B57 not determined.
- C. Brander notes this is a B\*5701 epitope.

**HXB2 Location** RT (244–252)

**Author Location** RT (244–252 LAI)

**Epitope** IVLPEKDSW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701, B\*5801)

**Keywords** binding affinity, rate of progression, escape

**References** Klein *et al.* 1998

- This peptide was defined as the optimal epitope.
- B57 has been associated with long-term non-progression in the Amsterdam cohort.
- The most pronounced CTL responses in HLA B\*5701 LTS were to RT and Gag.
- B57 restricted CTL responses are targeted at multiple proteins, but one LTS had a response that was dominated by reactivity to the epitope – two variants were found in this LTS: ITLPEKESW, which bound to B\*5701 with similar affinity as the index peptide but was an escape mutant that was not recognized by CTL, and IMLPEKDSW, which bound to B\*5701 with reduced affinity but could still be recognized.
- In an additional HIV+ LTS, only the variant IELPEKDSW was found, and this epitope was recognized by CTL but had less affinity for B\*5701 than the index peptide.
- This epitope was recognized in the context of both HLA-B\*5701 and B\*5801.

**HXB2 Location** RT (244–252)

**Author Location** Pol (244–252)

**Epitope** IVLPEKDSW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801)

**References** Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$

**HXB2 Location** RT (244–252)

**Author Location** RT (399–407)

**Epitope** IVLPEKDSW**Immunogen****Species (MHC)** human (B57)**References** van der Burg *et al.* 1997**HXB2 Location** RT (244–252)**Author Location** RT (244–252)**Epitope** IVLPEKDSW**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**Keywords** early-expressed proteins, kinetics**References** Guillon *et al.* 2002b

- An early-expressed Nef protein was modified to contain Env and Pol epitopes to enable the study the effect of expression kinetics on CTL mediated suppression of replication. The "EpiNef" construct was inserted into a recombinant vaccinia virus which was used to infect a target cell line; the target cells were lysed by CTL clones specific for the Env and Pol epitopes indicating that they were properly processed.

**HXB2 Location** RT (244–252)**Author Location** RT (244–252 ACH320.2A.2.1)**Epitope** IVLPEKDSW**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** (B57)**Keywords** acute/early infection, early-expressed proteins, kinetics**References** van Baalen *et al.* 2002

- Tat, Rev and Nef are the first HIV proteins expressed upon acute infection of T-cells (< 6 hours), and RT is not expressed until after 24 hours. The B14-restricted Rev-SAEPVPLQL specific CD8 T-cell clone TCC108, and the B57-restricted RT-IVLPEKDSW specific CD8 T-cell clone TCL1C11 were co-incubated with CD4+ cultures inoculated with HIV-1 at low MOI. Co-incubation with the Rev-specific CTL resulted in two logs less HIV-1 production in ten days of culture. When the RT epitope was cloned into the Nef gene of the infecting strain, another early expressed protein, it proved as effective as the Rev epitope at inhibiting viral production. A mathematical model of CTL-target interactions suggest early proteins are important for vaccine design.

**HXB2 Location** RT (244–252)**Author Location** Pol**Epitope** IVLPEKDSW**Epitope name** IW9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.

- One escape mutation, at position 2, was found in the most polymorphic residue in the epitope. This was shared between clades B and C. The position 2 mutation was significantly more common among persons expressing HLA-B57.

**HXB2 Location** RT (244–252)**Author Location** RT**Epitope** IVLPEKDSW**Epitope name** B57-IW9(RT)**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (244–252)**Author Location****Epitope** IVLPEKDSW**Immunogen** HIV-1 infection, vaccine*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease**Species (MHC)** human (B57)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** RT (244–252)**Author Location** Gag**Epitope** IVLPEKDSW**Epitope name** IW9**Subtype** B**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Australia, Canada, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** rate of progression, immunodominance, optimal epitope

**References** Streeck *et al.* 2007a

- To characterize HIV-1 proteome areas that are targeted in early, effective CTL responses, two cohorts were studied. Responses in early infection were against fewer epitopes and of lower magnitude than during chronic infection. While no region of the proteome was favored, Nef was the predominant target based on length of proteins. When based on the expression of protective versus nonprotective HLA I alleles, it was found that HLA-B27 and -57 possessing slow progressors to disease directed the majority of their responses to Gag in early infection, as opposed to those with HLA-B\*3501 or B\*3502, i.e. rapid progressors to AIDS, who had negligible responses to Gag. As compared with HLA-B57-/B27-subjects and HLA-B35 subjects, HLA-B57+/27+ subjects responded most to the p24 component of Gag. By using overlapping peptides within Gag p24, two were picked as being consistently targeted, and both contained previously described epitopes TW10 and KK10.
- IVLPEKDSW, i.e. epitope IW9 of RT protein was targeted in 62% of B57+ non-progressors to disease.

**HXB2 Location** RT (244–252)

**Author Location**

**Epitope** IVLPEKDSW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B57), an additional HLA (B58) was statistically predicted to be associated with this epitope.

**HXB2 Location** RT (244–252)

**Author Location**

**Epitope** IVLPEKDSW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Feeny *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

**HXB2 Location** RT (245–252)

**Author Location** Pol

**Epitope** IVPEKDSW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.

**HXB2 Location** RT (248–264)

**Author Location** (C consensus)

**Epitope** EKDSWTVNDIQKLVGKL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (259–267)

**Author Location** Pol

**Epitope** KLVGKLNWA

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.

- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNP to clear virus.
- This epitope can bind four of the five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).
- Tetramer staining with A2, beta2microglobulin, and either SLYNTVATL, KLVGKLNWA, or LTFGWCFKL revealed that tetramers detected more HIV-specific cells in LTNP than in progressors, activated effector cells were the minority population, and ELISPOT correlated better with the effector cell subpopulation than the total tetramer stained population.

**HXB2 Location** RT (260–271)  
**Author Location** RT (415–426 IIB)  
**Epitope** LVGKLNWASQIY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1501)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1501 epitope.

**HXB2 Location** RT (260–271)  
**Author Location** Pol (260–271)  
**Epitope** LVGKLNWASQIY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B15)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, escape  
**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. lvgkXnwasqiy variants arose at late time points

**HXB2 Location** RT (260–271)  
**Author Location** RT  
**Epitope** LVGKLNWASQIY  
**Epitope name** B15-LY12(RT)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B15)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (260–271)  
**Author Location** RT (415–426 IIB)  
**Epitope** LVGKLNWASQIY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B62)  
**References** Brander & Walker 1996; Menendez-Arias *et al.* 1998

- P. Johnson, pers. comm.

**HXB2 Location** RT (260–271)  
**Author Location** RT (260–271)  
**Epitope** LVGKLNWASQIY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B62)  
**Keywords** immunodominance  
**References** Day *et al.* 2001

- No immunodominant responses were detected to four B62-restricted epitopes tested.

**HXB2 Location** RT (260–271)  
**Author Location** Pol (415–426)  
**Epitope** LVGKLNWASQIY  
**Epitope name** LY12  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B62)  
**Donor MHC** A\*01, A\*11, B\*08, B\*15, Cw\*04, Cw\*07  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** escape, characterizing CD8+ T cells, optimal epitope  
**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The autologous form of the epitope, LVGKLNWASQIY, matched the B consensus throughout the 5-year period of study, with 1 rare variant at the first time point: LVGKLNWASQIh.

**HXB2 Location** RT (263–271)  
**Author Location** RT (263–271 LAI)  
**Epitope** KLNWASQIY

**Subtype B****Immunogen****Species (MHC)** human (A\*3002)**Keywords** optimal epitope**References** Frahm *et al.* 2008; Goulder *et al.* 2001a

- C. Brander notes this is an A\*3002 epitope.

**HXB2 Location** RT (263–271)**Author Location** RT**Epitope** KLNWASQIY**Epitope name** KY9 (RT-35)**Immunogen** HIV-1 infection**Species (MHC)** human (A\*3002)**References** Goulder *et al.* 2001a

- HLA-A\*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule.
- A rapid method was developed combining ELISPOT with intracellular IFN- $\gamma$  staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood.
- Two individuals were studied: Subject 199 (HLA A\*0201/\*3002 B\*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A\*3002/ B53/\*5801 Cw4/7) an African-Caribbean.
- In both HLA-A\*3002 individuals the response to RSLYNT-VATLY was dominant.
- In subject 199 four additional A\*3002 epitopes were identified.
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)

**HXB2 Location** RT (263–271)**Author Location** (C consensus)**Epitope** KLNWASQIY**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*3002)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** characterizing CD8+ T cells**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** RT (263–271)**Author Location** (C consensus)**Epitope** KLNWASQIY**Subtype C****Immunogen** HIV-1 infection**Species (MHC)** human (A\*3002)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- KLNWASQIY is an optimal epitope.

**HXB2 Location** RT (263–271)**Author Location** RT**Epitope** KLNWASQIY**Epitope name** A30-KY11(RT)**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A30)**Donor MHC** A30, A32, B18, B27**Keywords** HAART, ART, supervised treatment interruptions (STI)**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient D displayed the greatest response to B27-KK10 (p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

**HXB2 Location** RT (263–271)**Author Location** RT**Epitope** KLNWASQIY**Epitope name** A30-KIY9(RT)**Immunogen** HIV-1 infection**Species (MHC)** human (A30)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (266–285)**Author Location** Pol (421–440)**Epitope** WASQIYPGKIKVRQLCKLLRG**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** RT (268–282)**Author Location** RT (SF2)**Epitope** SQIYPGKIKVRQLCKL**Immunogen** HIV-1 infection**Species (MHC)** human**References** Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- RT peptides SQIYPGKIKVRQLCKL and WKG-SPAIFQSSMTKI were recognized.

**HXB2 Location** RT (269–277)**Author Location** (LAI)**Epitope** QIYPGKIKVR**Subtype** B**Immunogen****Species (MHC)** human (A\*0301)**Keywords** optimal epitope**References** Altfeld 2000; Frahm *et al.* 2008**HXB2 Location** RT (269–277)**Author Location** RT (269–277)**Epitope** QIYPGKIKVR**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Assay type** Other**Keywords** HLA associated polymorphism**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- QIYPGKIKVR was a previously defined A\*0301 presented epitope that encompassed an A\*03- associated polymorphism, QIYPGKIKVrIQ, in the last position. This epitope was embedded in a previously determined CTL immunoreactive region.

**HXB2 Location** RT (269–277)**Author Location** Pol (424–432)**Epitope** QIYAGIKVK**Subtype** B, CRF01\_AE**Immunogen** HIV-1 infection**Species (MHC)** human (A\*1101)**Keywords** binding affinity, subtype comparisons**References** Fukada *et al.* 2002

- binding affinity, inter-clade comparisons.
- Counterparts for eight known clade B HLA A\*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A\*1101 epitopes was recognized in a clade specific manner. Two other HLA A\*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- QIYAGIKVK is commonly found in viruses representing subtypes A, B and E. It was strongly recognized by CTL from 1/5 B clade infected Japanese subjects, and 5/7 E clade infected Thai subjects.
- QIYAGIKVK had the highest A\*1101 binding affinity, but qiyagikvR and qiyPgikvR (the most common C and D clade variant both bound to A\*1101). QIYAGIKVK and qiyagikvR were both cross-presented by a clone from a B clade infection, but qiyPgikvR was not.

**HXB2 Location** RT (269–277)**Author Location** (B consensus)**Epitope** QIYAGIKVK**Epitope name** QVK9**Immunogen** HIV-1 infection**Species (MHC)** human (A11)**Donor MHC** A02, A11, B18, B44, Cw12, Cw5**Country** United States**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** RT (269–277)

**Author Location** Pol (425–433)

**Epitope** QIYAGIKVK

**Epitope name** QK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** optimal epitope

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For one of the escape variants, a novel CD8 T-cell response equal in magnitude to the wild type, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wild type.
- This epitope did not vary.

**HXB2 Location** RT (269–277)

**Author Location** Pol (425–433)

**Epitope** QIYAGIKVK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** RT (269–277)

**Author Location** RT (269–277)

**Epitope** QIYPGIKVR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

**HXB2 Location** RT (269–277)

**Author Location** RT (424–432)

**Epitope** QIYPGIKVR

**Epitope name** A3-QR9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 4/7 individuals began to have detectable responses to this epitope after STI.

**HXB2 Location** RT (269–277)

**Author Location** RT (269–277)

**Epitope** QIYAGIKVK

**Epitope name** A3-QR9 Pol

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfield *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant qiyagikvR. The initial CTL response to both variants was strong but eventually declined, particularly to the variant in the second strain.

**HXB2 Location** RT (269–277)  
**Author Location** RT (269–277)  
**Epitope** QIYPGKIKVR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, escape  
**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** RT (269–277)  
**Author Location** Pol  
**Epitope** QIYPGKIKVK  
**Epitope name** QK9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A1, A3, B57, B7, Cw6, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 9, qiypgikvR, was found not to correspond to the most polymorphic residues in the epitope.

**HXB2 Location** RT (269–277)  
**Author Location** RT  
**Epitope** QIYPGKIKVR  
**Epitope name** A3-QR9(RT)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.

- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (271–279)  
**Author Location** (LAI)  
**Epitope** YPGIKVRQL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*4201 epitope.

**HXB2 Location** RT (271–279)  
**Author Location** (C consensus)  
**Epitope** YPGIKVRQL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** RT (271–279)  
**Author Location** (C consensus)  
**Epitope** YPIGKVRQL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.



- Mutational patterns in the L9 residue of YPIGKVRQL are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** RT (271–279)

**Author Location** RT (271–279)

**Epitope** YPGIKVRQL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201)

**Assay type** Other

**Keywords** HLA associated polymorphism

**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- YPGIKVRQL was a previously defined B\*4201 presented epitope that encompassed an B\*42 associated polymorphism, YpGIKVRQL, in the second position. This epitope was found embedded in a previously determined immunoreactive region.

**HXB2 Location** RT (271–279)

**Author Location** RT (271–279)

**Epitope** YPGIKVRQL

**Epitope name** YL9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other

**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism

**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- A strong association between B\*4201 and variation in the epitope was found.

**HXB2 Location** RT (271–279)

**Author Location**

**Epitope** YPGIKVKQL

**Epitope name** YL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201)

**Country** South Africa

**Assay type** proliferation, Tetramer binding, Intracellular cytokine staining

**References** Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

**HXB2 Location** RT (271–279)

**Author Location** (C consensus)

**Epitope** YPIGKVRQL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4202)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the L9 residue of YPIGKVRQL are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** RT (271–279)

**Author Location** RT (438–446 IIIB)

**Epitope** YPGIKVRQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B42)

**Keywords** responses in children, mother-to-infant transmission

**References** Menendez-Arias *et al.* 1998; Wilson *et al.* 1996

- YAGIKVRQL and YPGIKVKQL are naturally occurring variants that are both reactive.
- YHKIKVRQL is a naturally occurring variant that has not been tested.
- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

**HXB2 Location** RT (271–279)

**Author Location** Pol (438–446 IIIB)

**Epitope** YPGIKVRQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B42)

**Keywords** mother-to-infant transmission, escape

**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.

- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- An additional variant that gave a positive CTL response: YPGIKVKQL, YAGIKVRQL.
- YHGKVRQL was an escape mutant.

**HXB2 Location** RT (271–279)

**Author Location**

**Epitope** YPGIKVRQL

**Epitope name** YL9 ?

**Immunogen** HIV-1 infection

**Species (MHC)** human (B42)

**Country** United States, South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** memory cells

**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** RT (271–279)

**Author Location**

**Epitope** YPGIKVRQL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120 boost, polyepitope *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human

**Donor MHC** A\*3001, A\*3002; B\*4201/02, B\*4403/26/30

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** RT (293–301)

**Author Location** RT (448–456 SF2)

**Epitope** IPLTEEAEL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**References** Menendez-Arias *et al.* 1998; Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- Only 1/7 B35-positive individuals had a CTL response to this epitope.
- An E to K substitution at position 5 abrogates specific lysis, but not binding to B\*3501.
- An I to V substitution at position 1, P to Q at position 2, and E to K at 5, abrogates specific lysis and binding to B\*3501.
- An I to V substitution at position 1 did not alter reactivity.
- Reviewed in Menendez-Arias *et al.* [1998], this epitope lies in the thumb region of RT.

**HXB2 Location** RT (293–301)

**Author Location** Pol (HXB2, LAI)

**Epitope** IPLTEEAEL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**Donor MHC** A\*2402, A\*2601, B\*3501, B\*5101

**Country** Japan

**Assay type** Cytokine production, Tetramer binding, Chromium-release assay

**Keywords** binding affinity, kinetics, TCR usage, characterizing CD8+ T cells, immune dysfunction

**References** Ueno *et al.* 2004b

- Two different clonotypes of CD8+ T-cells with specificity for this epitope were isolated from a chronic HIV+ patient. The clonotype with the relatively high affinity TCR had no cytolytic activity, cytokine production or proliferation in response to HIV-infected cells, while the moderate affinity clonotype had strong reactions. More than 3-fold increased duration in tetramer 1/2 life was observed with the defective clonotype. The TCRs from the two clonotypes preserved the phenotype when transduced into primary CD8+ T cells, suggesting the TCR with higher affinity was directly associated with impaired T-cell reactivity of the cells.
- The high affinity impaired TCR was Valpha1.1/Vbeta13.3, the moderate affinity active TCR was Valpha12.1/Vbeta5.6.

**HXB2 Location** RT (293–301)

**Author Location** Pol (HXB2, LAI)

**Epitope** IPLTEEAEL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1501, B\*3501)

**Donor MHC** A\*2402, A\*2601, B\*3501, B\*5101

**Country** Japan

**Assay type** Cytokine production, Tetramer binding, Chromium-release assay

**Keywords** binding affinity, cross-presentation by different HLA, immunotherapy, TCR usage, characterizing CD8+ T cells

**References** Ueno *et al.* 2004a

- This paper described the transduction of HIV specific clone TCR genes Valpha12.1/Vbeta5.6 into primary CD8+ T cells. Epitope fine specificity and appropriate effector functions were observed in the transduced cells, although functional avidity could change due to different densities of TCR on the surface of the transduced cells. No allogenic responses were detected. This methodology could have immunotherapeutic applications.

**HXB2 Location** RT (293–301)

**Author Location** Pol (448–456 SF2-24)

**Epitope** IPLTEEAEL

**Epitope name** HIV-B35-SF2-24

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501, B\*5101)

**References** Tomiyama *et al.* 2000b

- This epitope is naturally processed and presented by both HLA-B\*3501 and HLA-B\*5101 and is cross-recognized by a single CTL clone.
- IPLTEEAEL binds approximately four times more tightly to HLA-B\*3501 than HLA-B\*5101.

**HXB2 Location** RT (293–301)

**Author Location** Pol (489–456)

**Epitope** IPLTEEAEL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702, B\*3501, B\*5101, B\*5301)

**Donor MHC** A24, A26, B35, B51, Cw3

**Keywords** supertype, cross-presentation by different HLA, TCR usage

**References** Ueno *et al.* 2002

- The IPLTEEAEL epitope was known to be presented by both HLA-B\*3501 and -B\*5101 to a dual specific CTL clone. A single TCR complex bearing Valpha12.1 and Vβ5.6 was shown recognize the epitope in either HLA-B\*3501 and -B\*5101. Furthermore, this TCR also recognized the peptide presented by B\*5301 and B\*0702 in cytolytic CTL assays, demonstrating that this single TCR complex recognizes the same peptide presented by a range of HLA class I molecules.

**HXB2 Location** RT (293–301)

**Author Location** (SF2)

**Epitope** IPLTEEAEL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** rate of progression

**References** Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals but this was one of the six that had no B35 associated pattern of mutation.

**HXB2 Location** RT (293–301)

**Author Location** RT (448–456 SF2)

**Epitope** IPLTEEAEL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35, B51)

**References** Menendez-Arias *et al.* 1998; Shiga *et al.* 1996

- Binds HLA-B\*3501 and B\*5101.
- Reviewed in Menendez-Arias *et al.* [1998], this epitope lies in the thumb region of RT.

**HXB2 Location** RT (293–301)

**Author Location** Pol (447–455)

**Epitope** IPLTEEAEL

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B51)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** RT (293–301)

**Author Location** RT (293–301)

**Epitope** IPLTEEAEL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** RT (293–301)

**Author Location** RT Pol (286–294)

**Epitope** IPLTEEAEL

**Epitope name** IPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52

**Assay type** CD8 T-cell Elispot - IFNγ, Tetramer binding, CD4 T-cell Elispot - IFNγ

**Keywords** rate of progression, immunodominance, escape

**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- The IPL epitope was found to be under positive selection for escape mutations and it was replaced by first variant between days 297 and 369, ipltGaeI. This new variant was subsequently replaced by 2 further variants, that were even more resistant to CD8+ T cell recognition between days 369 and 635, ipltAeaeI and ipltVeaeI.

**HXB2 Location** RT (294–318)

**Author Location** RT (461–485 HXB2)

**Epitope** PLTEEALELAENREILKEPVHGVY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Menendez-Arias *et al.* 1998; Walker *et al.* 1989

- One of five epitopes defined for RT-specific CTL clones in this study.

**HXB2 Location** RT (298–312)

**Author Location** RT (291–305)

**Epitope** EAELELAENREILKE

**Epitope name** EAE

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, escape

**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive peptides found not to vary over time. It was one of four epitopes that were not precisely defined.

**HXB2 Location** RT (302–319)

**Author Location** RT

**Epitope** ELAENREILKEPVHGVY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This overlapping peptide, ASRELERFAVNPGLL, was differentially targeted across ethnic groups and had an overall frequency of recognition of 13.3% - 6.8% AA, 26.9% C, 20.5% H, 0% WI (P value = 0.0028).

**HXB2 Location** RT (302–319)

**Author Location** (C consensus)

**Epitope** ELAENREILKEPVHGVY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0202)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (308–317)

**Author Location** RT (LAI)

**Epitope** EILKEPVGHV

**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**References** Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997
- Recognized by CTL from a long-term survivor, SPI-ETVPVKL was also recognized.
  - Recognized by CTL from a progressor, EELRQHLLRW and TWETWWTEYW were also recognized.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Keywords** HAART, ART

**References** Huang *et al.* 2000

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed.
- Increases in gamma interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-gamma-production ELISPOT.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Keywords** HAART, ART

**References** Rinaldo *et al.* 2000

- Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that persist after therapy and long periods of virus being below the level of detection.

**HXB2 Location** RT (309–317)

**Author Location** RT

**Epitope** ILKEPVHGV

**Epitope name** IV9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Keywords** HAART, ART, immunodominance

**References** Scott-Algara *et al.* 2001

- This study examined with CTL response in HLA A\*02+ children by tetramer staining for HLA-A2 immunodominant epitopes SLYNTVATL and ILKEPVHGV.
- 71% of the 28 HIV-1 infected HLA-A\*02 positive children recognized both epitopes, with cells from 26 children stained positive by the gag tetramer (SLYNTVATL) and 21 children by the pol tetramer (ILKEPVHGV)
- There were no differences observed in children that had therapy versus those that did not.
- Tetramer-binding cells were memory activated CD28-, CD45RO+, CD45RA- HLADR+, CD69-, CD8+ T-cells.

**HXB2 Location** RT (309–317)

**Author Location** RT

**Epitope** ILKEPVHGV

**Epitope name** POL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** France

**Assay type** Cytokine production, Tetramer binding, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** responses in children, characterizing CD8+ T cells

**References** Scott-Algara *et al.* 2005

- Only a fraction of HIV-1-specific CD8 T-cells detected in the PBMC of 17 infected children (ages 2-18) were able to produce cytokines (IFN-gamma, TNF-alpha) or chemokines (CCL4, CCL5) after stimulation with the cognate peptide. A negative correlation was found between the plasma viral load and the percentage of CD8+ Gag-specific T-cells secreting IFN-gamma. Tetramers used in this study were SLYNTVATL-HLA-A\*02 and ILKEPVHGV-HLA-A\*02.

**HXB2 Location** RT (309–317)

**Author Location** RT (309–317)

**Epitope** ILKEPVHGV

**Epitope name** IV9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- Responses to epitope IV9 were seen in early chronic infection.

**HXB2 Location** RT (309–317)

**Author Location** RT (309–317)

**Epitope** ILKEPVHGV

**Epitope name** IV9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Assay type** CTL suppression of replication

**Keywords** class I down-regulation by Nef

**References** Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein RT epitope ILKEPVHGV-recognizing CTLs were affected by Nef.

**HXB2 Location** RT (309–317)

**Author Location** Protease-RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection, in vitro stimulation or selection

**Species (MHC)** human (A\*02)

**Assay type** Other

**Keywords** kinetics

**References** Wick *et al.* 2005

- Experimental and mathematical models were used to estimate the number of HIV-infected cells that can be killed by CD8+ T-cells. On average, CTLs can kill from 0.7 to 3.0 cells/day.
- CTL clone 68A62 recognizes epitope ILKEPVHGV and was used to study the inhibition of HIV-1 replication in acutely infected cells in vitro.

**HXB2 Location** RT (309–317)

**Author Location**

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** acute/early infection

**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T cells and viral load.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWILGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Spiegel *et al.* 2000

- High levels of CD8+ HIV-1 specific and cytomegalovirus specific CTL were detected by HLA-A\*0201-peptide tetramers in 3 infected subjects with very low CD4 counts, but CD8 T cell mediated effector activity was not seen.
- Thus HIV-1 specific CD8+ cells may be present but may lack direct effector activity in late disease, suggesting that over-coming antigen unresponsiveness may be a useful therapeutic strategy.

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** epitope processing, immunodominance

**References** Sewell *et al.* 1999

- Proteasome regulation influences epitope processing and could influence immunodominance.
- The proteasome is inhibited by lactacystin treatment, and gamma IFN induces expression of proteasome subunits, LMP2 and LMP7, which combine with the proteasome to create an immunoproteasome.
- IFN-gamma induction of the immunoproteasome and lactacystin inhibition increases the presentation of the A\*0201 VIYQYMDDL epitope, but decreases the presentation of the A\*0201 ILKEPVHGV epitope, which is immunodominant within pol proteins, showing the two epitopes are processed by different pathways.
- ILKEPVHGV seems to be processed by the classical proteasome pathway, while VIYQYMDDL appears to be destroyed by this pathway.
- This epitope contains the catalytic site (YMDD) of RT, a conserved sequence in HIV-1 which restricts escape mutants.

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** epitope processing

**References** Loing *et al.* 2000

- The ILKEPVHGV was modified by the addition of an N-palmitoyl-lysine residue at the P0, P1 or P10 positions of the parent peptide to create a lipopeptide for direct antigen delivery to the cytoplasm for processing.
- The N-terminal modification increased the life span for functional CTL recognition up to 48 hours in comparison to the parent peptide.

**HXB2 Location** RT (309–317)

**Author Location** Pol (510–518)

**Epitope** ILKEPVHGV

**Immunogen** vaccine

*Vector/Type:* canarypox, vaccinia *HIV component:* Env, Gag, Nef, Pol

**Species (MHC)** human (A\*0201)

**References** Larsson *et al.* 1999

- ELISPOT was used to assay the CD8 T cell response to the HIV-1 proteins Gag, Pol, Nef or Env expressed in vaccinia or canarypox vectors in 19 HIV+ people.
- The highest CTL frequency was directed at epitopes in Pol.
- In A\*0201 individuals, higher numbers of spot-forming T cells were directed against HIV-1 proteins expressed in vaccinia than to peptides SLYNTVATL and ILKEPVHGV presented by A2.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** TCR usage

**References** Wilson *et al.* 1998a

- HIV+ individuals were followed longitudinally using MHC tetramers in combination with 14 anti-BV chain MAbs, and clonal expansion of HIV-specific T cells was followed *in vivo*.
- Seven HIV+ people were studied, and all showed expansions of particular TCR BV clones, often several, relative to uninfected controls.
- Three patients were followed in detail, TCR VB expansions persisted for 2 to 3 years, with occasional transient increases.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 2/11 of the A2+ individuals responded to ILKEPVHGV, and neither of these two responded to SLYNTVATL.

**HXB2 Location** RT (309–317)

**Author Location** Pol

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** HAART, ART

**References** Gray *et al.* 1999

- Administration of highly active antiretroviral therapy (HAART) reduced CD8+ cell frequency, and the CD8+ cells detected by tetramer staining were likely to be memory cells, indicating that persistently replicating viral populations are needed to maintain high frequencies of HIV-1 specific CTL.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Menendez-Arias *et al.* 1998; Ogg *et al.* 1998b

- HLA-tetrameric complexes were used in a cross-sectional study of 14 untreated HLA A\*0201 positive individuals, revealing an inverse relationship between HIV Gag and Pol specific CTL effector cells (CTLe) and viral load.
- Inclusion of both the p17 SLYNTVATL and RT ILKEPVHGV epitopes gives a good representation of HLA A\*0201-restricted activity.
- No correlation was observed between the CTLe and CD4 count or clearance rate of productively infected cells.

**HXB2 Location** RT (309–317)

**Author Location** RT

**Epitope** ILKEPVHGV

**Immunogen** vaccine

*Vector/Type:* vaccinia

**Species (MHC)** human (A\*0201)

**References** Hanke *et al.* 1998a; Hanke *et al.* 1998b

- This epitope was shown to be processed and presented to appropriate CTL clones upon infection of human target cells with vaccinia virus Ankara (VVA) carrying 20 HIV-1 epitopes recognized by humans.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity

**References** Konya *et al.* 1997; Menendez-Arias *et al.* 1998

- This epitope was included as a positive control.
- Binding affinity to A\*0201 was measured,  $C_{1/2 \max} \mu\text{M} = 12$ .

**HXB2 Location** RT (309–317)

**Author Location** RT (468–476)

**Epitope** ILKEPVHGV

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (A\*0201)

**References** van der Burg *et al.* 1996

- Immunogenic in humans, slow dissociation rate, and associated with immunogenicity in transgenic HLA-A\*0201/K<sup>b</sup> mice.
- CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual.

**HXB2 Location** RT (309–317)

**Author Location** RT (468–476)

**Epitope** ILKEPVHGV

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (A\*0201)

**References** van der Burg *et al.* 1995

- Binds HLA-A\*0201 – CTL generated by *in vitro* stimulation of PBMC from an HIV negative donor.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Menendez-Arias *et al.* 1998; Pogue *et al.* 1995

- Mutational study: position 1 I to Y increases complex stability with HLA-A\*0201.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** review, escape

**References** Goulder *et al.* 1997e; Goulder *et al.* 1997a; Menendez-Arias *et al.* 1998

- HLA-identical sibling hemophiliac brothers were both infected with the same batch of factor VIII.
- One had a response to gag A2 epitope SLYNTVATL, the other to pol A2 epitope ILKEPVHGV. They were tested 6–8 years after infection.
- Viral sequencing from the twin that had no response to SLYNTVATL indicated his virus had the substituted form SLHNAVAL.
- 71% of an additional set of 22 HIV-1 infected HLA-A\*0201 positive donors preferentially responded to gag SLYNTVATL.
- Those individuals with a pol ILKEPVHGV response tended to have mutations in or around SLYNTVATL.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

**HXB2 Location** RT (309–317)

**Author Location** RT (309–317)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Altman *et al.* 1996

- This paper introduces the tetramer methodology which permits quantification of specific CTL based on expression of specific TCRs—HLA-A2 tetramers were prepared that can stain CTL lines specific for ILKEPVHGV and SLYNTVATL, and can quantify HIV-specific CD8+ cell lines in freshly isolated PBMCs.
- Three patients only stained the Gag epitope SLYNTVATL, one patient had the highest frequency of tetramer staining to the Pol epitope (0.77%), less to the Gag epitope (0.28%)
- The A2-Pol CD8+ clones were CD45RO positive and HLA-DR and CD38 negative, suggesting a memory rather than effector phenotype.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A\*0201)

**Keywords** epitope processing

**References** Menendez-Arias *et al.* 1998; Walter *et al.* 1997

- HLA-A2 heavy chain and  $\beta$ 2-microglobulin expressed in *E. coli* were refolded in the presence of this peptide.
- The HLA-A2-peptide complex elicited HLA-A2 peptide-specific CTL response in cells lacking HLA-A2.

- Suggests that preformed HLA-peptide complexes could provide an alternate to intracellular processing for immunogens.

**HXB2 Location** RT (309–317)

**Author Location** RT (464–472)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** HAART, ART

**References** Gray *et al.* 1999

- Peptide-tetramer complexes of A\*0201 and SLYNTVATL or ILKEPVHGV were used to study individuals receiving HAART to determine the frequency of Class I HLA-restricted anti-HIV CD8+ T cells.
- 17/18 asymptomatic patients had a CTL response to one or both epitopes – 72% had a CTL response to SLYNTVATL.
- After HAART, the majority of the epitope-specific CTL were apparently memory cells.

**HXB2 Location** RT (309–317)

**Author Location** Pol

**Epitope** ILKEPVHGV

**Immunogen** vaccine

*Vector/Type:* DNA

**Species (MHC)** transgenic mouse (A\*0201)

**References** Ishioka *et al.* 1999

- A minigene vaccine construct encoding 6 HLA 2.1 and 3 HLA A11 restricted CTL epitopes, the universal Th cell epitope PADRE (pan-DR epitope) and an ER translocating signal sequence was constructed.
- The epitopes were chosen for dominant recognition by CTLs during HBV and HIV infections in humans.
- HLA transgenic mice were used for quantitating *in vivo* immunogenicity of DNA vaccines encoding HLA-restricted CTL epitopes – strong responses were observed to all nine epitopes, and CTL memory persisted up to four months after a single injection.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** escape

**References** Brander *et al.* 1998a

- Of 17 infected HLA A\*0201 subjects, 13 had CTL responses against the p17 SLYNTVATL epitope, six recognized ILKEPVHGV and five recognized VIYQYMDDL, and there was no correlation between viral load and recognition of a specific epitope or evidence of immune escape.
- Only one subject had CTL against all three epitopes.
- Subjects were part of the San Francisco City Clinic Cohort, the ARIEL project and from the Boston area.
- C. Brander notes this is an A\*0201 epitope.

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)



**Keywords** HAART, ART

**References** Ogg *et al.* 1999

- CTL effector levels were measured after potent ARV therapy using HLA-tetramer complexes for the A\*0201 epitopes SYLVTVATL and ILKEPVHGV in seven patients, and the B\*3501 epitope DPNPQEVVL in one additional patient.
- Levels of CTL effectors typically decline for 5-7 days and then rebound, fluctuating during the first two weeks of therapy.
- After the early fluctuation, there was a steady exponential decay with a median half-life of 45 days.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484 LAI)

**Epitope** ILKEPVHGV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a A\*0201 epitope.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Epitope name** IV9

**Immunogen** HIV-1 infection, *in vitro* stimulation or selection

**Species (MHC)** human (A\*0201)

**References** Dela Cruz *et al.* 2000

- Integration of HIV RT CTL epitopes into the N-terminus of the HLA-A2 heavy chain, or tethering the epitopes to the target chain, resulted in epitope-specific lysis by CD8+ CTL.
- These antigens could also be used to stimulate primary responses *in vitro*.

**HXB2 Location** RT (309–317)

**Author Location** RT (309–317)

**Epitope** ILKEPVHGV

**Epitope name** P1

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** HAART, ART, escape

**References** Samri *et al.* 2000

- The epitope was recognized by patient 250#0 but not in another A\*0201+ patient, 201#5, in a study of the effects of therapy escape mutations on CTL recognition.

**HXB2 Location** RT (309–317)

**Author Location** Pol (LAI)

**Epitope** ILKEPVHGV

**Subtype** B

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (A\*0201)

**Keywords** dendritic cells

**References** Engelmayer *et al.* 2001

- Recombinant canarypox virus vector containing HIV-1 sequences, upon infection of mature dendritic cells, can trigger specific lysis through *in vitro* by T-cells from HIV-1 infected individuals at levels comparable to the response seen to HIV carried in vaccinia vectors.

- Recombinant canarypox virus vector containing HIV-1 sequences can also stimulate HIV-specific CD4+ helper T-cell responses.

**HXB2 Location** RT (309–317)

**Author Location** Pol

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Gea-Banacloche *et al.* 2000

- In a study including many long-term non-progressors, no correlation between plasma virus levels and number of HIV-specific CD8+ T-cells was found.
- High frequencies of circulating CD8+ T-cells were HIV-1 specific, and the majority of these responses were to gag-pol gene products.
- 4/21 subjects were HLA-(A\*0201), and of these only 2 subjects (patient 3 and 19) tested positive to this epitope.

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** HAART, ART, rate of progression

**References** Jin *et al.* 2000a

- The CTL effector levels (CTLe) were compared in long term non-progressors (LTNP) with low viral load and in patients whose virus was well-suppressed by therapy, using a tetramer assay.
- LTNPs have high memory CTLe numbers and low viral load, while HAART patients had low CTLe numbers and low viral load.

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$

**HXB2 Location** RT (309–317)

**Author Location** Pol

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** dendritic cells

**References** Ostrowski *et al.* 2000

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*

- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T cell help in 9 of 10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T cell help to a variable degree in most of patients.
- Those CTL that didn't respond to CD40LT could expand with IL2 present, and IL15 produced by dendritic cells also contributes.
- The T-helper epitope used for CD4+ T cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKAN-SKFIGITE)

**HXB2 Location** RT (309–317)

**Author Location** RT (309–317)

**Epitope** ILKEPVHGV

**Epitope name** RT2

**Immunogen** vaccine

*Vector/Type:* HIV-1 peptide in filamentous bacteriophage major coat protein *HIV component:* RT

**Species (MHC)** human, transgenic mouse (A\*0201)

**References** Guardiola *et al.* 2001

- HLA-A2 transgenic mice were injected with bacteriophage antigens expressing a Th epitope and the HIV CTL epitope ILKEPVHGV, and epitope-specific cytotoxic activity was induced.

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** epitope processing, immunodominance

**References** Sewell *et al.* 2002

- Epitope processing of three different HLA-A\*0201 HIV epitopes was shown to use different pathways, which might influence patterns of immunodominance. .174 cells were used that lack TAP1 and TAP2 genes, as well as the LMP2 and LMP7 genes that encode the beta-subunits of the immunoproteasome. These genes could be added back through transfection to study processing.
- ILKEPVHGV was efficiently presented in TAP-1 and -2 transfected cells while VIYQYMDDL and SLYNTVATL were not. VIYQYMDDL was destroyed by the MB1 subunit of the protease, and could be expressed in the presence of the proteasome inhibitor lactacystin, but SLYNTVATL expression was not restored. SLYNTVATL expression was unaltered by lactacystin in a wild type cell line.

**HXB2 Location** RT (309–317)

**Author Location** Pol

**Epitope** ILKEPVHGV

**Epitope name** IL-9

**Immunogen** HIV-1 infected monocyte-derived

**Species (MHC)** mouse (A\*0201)

**References** Poluektova *et al.* 2002

- Nonobese diabetic NOD-C.B-17 SCID mice were reconstituted with HLA-A\*0201 positive human PBL and injected with HIV-1 infected monocyte-derived macrophages MDM in the basal ganglia to provide a mouse model of HIV-1 encephalitis.
- HLA-A\*0201 CTL responses were detected by tetramer staining in the spleen in seven days, increased through day 14, and the numbers of productively infected were reduced >85% in the second week.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484 LAI)

**Epitope** ILKEPVHGV

**Epitope name** LR22

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG

**Species (MHC)** mouse (A\*0201)

**Keywords** binding affinity, vaccine-specific epitope characteristics, immunodominance

**References** Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEGAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRAFTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a strong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484 LAI)

**Epitope** ILKEPVHGV

**Epitope name** LR22

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12, P30

**Species (MHC)** mouse (A\*0201)

**Keywords** vaccine-specific epitope characteristics, immunodominance

**References** Peter *et al.* 2002

- When HIV-1 peptides were used to vaccinate HLA-A2.1 transgenic A2-Kb mice, strong responses to five peptides were observed when the peptides were given individually, but immunodominance limited the response to some of the peptides when they were given in combination Peter *et al.* [2001]. IL-12 can counteract immunodominance in BALB/c mice, so it

was given with the multiple epitope vaccination, and was instead found to specifically eliminate the HLA-A2.1-epitope CTL responses, but not Kb CTL responses. This was possibly a consequence of transient depletion of T-cells, B cells and macrophages in the spleen.

**HXB2 Location** RT (309–317)

**Author Location** RT (309–317)

**Epitope** ILKEPVHGV

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* RT  
*Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** transgenic mouse (A\*0201)

**Keywords** binding affinity, vaccine-specific epitope characteristics

**References** Boissonnas *et al.* 2002

- Ten naturally occurring variants of the Nef epitope VLMWQFDSRL were tested for their affinity to HLA-A\*0201 and for their ability to induce gamma-IFN and cytotoxic functions through vaccination of HLA-A\*0201 transgenic mice.
- ILKEPVHGV could induce HLA-A\*0201 vaccine responses, and was a positive control.

**HXB2 Location** RT (309–317)

**Author Location** Pol (468–476)

**Epitope** ILKEPVHGV

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* HIV-1

**Species (MHC)** mouse (A\*0201)

**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Singh *et al.* 2002; Sykes & Johnston 1999

- C3H (H-2k) transgenic mice carrying a fused HLA-A\*0201 alpha1 and alpha2 and H-2Dk alpha3 hybrid class I molecule were immunized using an epidermal gene gun with an ubiquitin expression library of 32 plasmids that spanned the HIV-1 genome. Ubiquitin targets the expressed HIV-1 peptides to the proteasome.
- A single immunization with the UB-HIV-1 library vaccine induced potent, stable and multivalent CTL responses against all library members.
- Immunodominant epitopes SLYNTVATL (Gag), ILKEPVHGV (Pol), RIQRGPGRAFTIGK (Env) and AFHHVAREK (Nef) elicited strong CD8+/IFN- responses and stimulated CTL that were functional in a Cr-release assay and against wild type antigen.
- The presence of multiple plasmids HLA-A\*0201-restricted CTL epitopes did not decrease CTL immunogenicity, and CTL responses to single peptide immunizations were comparable to responses based on mixtures of either 16 or 32 peptides.

**HXB2 Location** RT (309–317)

**Author Location** Pol

**Epitope** ILKEPVHGV

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human, macaque (A\*0201)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFNgamma Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A\*0201)

**Keywords** epitope processing, dendritic cells

**References** Andrieu *et al.* 2003

- This study demonstrates that lipopeptides carrying epitopes can be taken up by human dendritic cells, processed using different pathways, and recognized by epitope-specific CD8+ T-cells originally derived from HIV+ individuals. The RT ILKEPVHGV peptide was embedded in a longer peptide fragment in the lipopeptide, and was internalized by endocytosis and processed in the cytosol by proteasomal cleavage by following an endosome-to-cytosol pathway for processing and presentation. Administration of epoxomicin, a proteasome inhibitor, completely abrogated epitope presentation to a CD8+ T-cell line, while monensin, an inhibitor of acid-dependent endosomal enzyme activity did not.
- In contrast to the RT epitope, dendritic cell presentation of the Nef epitope QVPLRPMTYK embedded in a longer peptide in a lipopeptide was not inhibited by epoxomicin, but was inhibited by monensin, indicative of endocytotic epitope processing.

**HXB2 Location** RT (309–317)

**Author Location**

**Epitope** ILKEPVHGV

**Epitope name** IV9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, proliferation, Tetramer binding, Intracellular cytokine staining, Chromium-release assay

**References** Dagarag *et al.* 2003

- Telomer length is short in the CD8+ T-cell compartment of HIV-1 infected people, indicating excessive CTL activation and premature senescence. Here human telomerase RT (hTERT) transduction of HIV-1-specific CTL was used to study the functional impact of telomerase. Telomerase expression enhanced proliferative capacity, as well as cytolytic and antiviral capabilities; cytokine production was unchanged. hTERT transduced CTLs were 10-fold more efficient in controlling HIV-1 replication in culture. Thus telomerase transduction can restore CTL mediated cytolysis, and may have therapeutic potential.
- Three polyclonal CD8+ T-cell lines derived from an HIV-1, HLA A\*0201 positive patient were used in this study, including one specific for this epitope. An IV9-specific monoclonal cell line, 68A62 was also generated.

**HXB2 Location** RT (309–317)

**Author Location** Pol (464–472)

**Epitope** ILKEPVHGV

**Epitope name** I9V

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* RT  
*Adjuvant:* CpG immunostimulatory sequence (ISS)

**Species (MHC)** transgenic mouse (A\*0201)

**Donor MHC** H-A2/Kb

**Assay type** Cytokine production, Tetramer binding, Intracellular cytokine staining, Chromium-release assay

**References** Daftarian *et al.* 2003

- HLA-A\*0201 transgenic mice were immunized with a Th-CTL-fusion peptide composed of the I9V CTL epitope linked to the promiscuous PADRE Th epitope. The peptide only when given in combination with CpG elicited strong I9V-CTL responses.
- The peptide-CpG vaccinated mice, when challenged with pol embedded in vaccinia (pol-vv), could clear the virus from the ovaries. Additionally, intranasal immunized mice given an intranasal pol-vv challenge reduced virus in the lungs.

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV

**Epitope name** IV9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** Tetramer binding

**Keywords** genital and mucosal immunity

**References** Shacklett *et al.* 2003

- Lymphocytes from rectal biopsies were used to characterize the CD8+ T cell response to HIV in GALT, Gut-associated lymphoid tissues. Patients were selected on the basis of being HLA-A2+ and having detectable SLYNTVATL and ILKEPVHGV tetramer responses in PBMC. SLYNTVATL

frequency was increased in GALT relative to PBMC in 6/7 patients studied, while a control response to a CMV-peptide was diminished in GALT. Only two patients had ILKEPVHGV CD8+ T cell responses, and both had slightly higher frequencies in GALT than PBMC.

- HIV may perturb lymphocyte retention in GALT, suggested by an overall reduction of GALT CD8+ cells expressing alphaEbeta7. GALT HIV-specific CD8+ T cells expressed alphaEbeta7, suggesting mucosal priming.

**HXB2 Location** RT (309–317)

**Author Location** RT (309–317 MN)

**Epitope** ILKEPVHGV

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, polyepitope *Strain:* B  
*clade MN HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** humanized mouse (A\*0201)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy

**References** Isagulians *et al.* 2004

- Immunization of HLA-A\*0201-transgenic mice with synthetic genes encoding clusters of human A\*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains.
- This was one of five HLA-A\*0201 epitopes from the RT or protease proteins that was included in the polyepitope vaccine. When the transgenic HLA A\*0202 mice were vaccinated with the polyepitope construct or with a mixture of RT peptides, a sustained low level CD8+ T-cell gamma IFN response was observed, in contrast to when an intact RT gene was used for vaccination.

**HXB2 Location** RT (309–317)

**Author Location**

**Epitope** ILKEPVHGV

**Epitope name** IV9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , T-cell Elispot, Flow cytometric T-cell cytokine assay

**Keywords** epitope processing, escape, kinetics, variant cross-recognition or cross-neutralization

**References** Jamieson *et al.* 2003

- Epitope escape mutations in chronically infected individuals developed over several years indicating slight selective advantage of escape mutants. The maturation state of CTLs appear to affect the rate of epitope mutation and CTL decay.
- In two patients, IV9 mutations preceded the loss of IV9-specific CD8+ T-cells. In a third patient, escape mutations were coincident with IV9-specific CD8+ T-cell loss. One patient was infected with a ilepvhgA variant, and transiently reverted to the consensus form at year 3. One patient never made

a response to IV9 despite being infected with the consensus form of the epitope.

**HXB2 Location** RT (309–317)  
**Author Location** Gag  
**Epitope** ILKEPVHGV  
**Epitope name** IV9  
**Subtype** B  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (A\*0201)  
**Assay type** Tetramer binding, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** epitope processing, rate of progression, immunodominance, acute/early infection, dendritic cells, TCR usage, memory cells  
**References** Kan-Mitchell *et al.* 2004

- In contrast to IV9-CTLs, SL9-CTLs were shown to be primed by immature DCs and to be independent of help from CD4+ or exogenous IL2 and sensitive to paracrine IL-2-induced apoptosis.

**HXB2 Location** RT (309–317)  
**Author Location** Pol (468–476 IIBB)  
**Epitope** ILKEPVHGV  
**Epitope name** pol468-476  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade IIBB  
*HIV component:* Gag-Pol  
**Species (MHC)** humanized mouse (A\*0201)  
**Assay type** Intracellular cytokine staining  
**Keywords** epitope processing, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization, vaccine antigen design  
**References** Singh & Barry 2004

- When A\*0201-C3H/J transgenic mice were immunized with plasmids encoding wild-type gag-pol, codon-optimized (CO) gag-pol, and an expression library vaccine expressing 16 fragments of gag-pol fused with ubiquitin for proteasome targeting (ELI), the ELI vaccine produced up to 10-fold higher CD8 T-cell responses than the other two vaccines. In contrast to the wt and CO vaccines, which tended to augment only immunodominant responses, boosting with the ELI vaccine resulted in many CD8 responses against variant epitopes from different HIV-1 clades, and against drug-resistant variants.
- This epitope was recognized in transgenic mice vaccinated with all three vaccine constructs, but the most intense responses were to the ELI vaccine.

**HXB2 Location** RT (309–317)  
**Author Location** Pol (464–472)  
**Epitope** ILKEPVHGV  
**Epitope name** IV9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06  
**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** escape, acute/early infection

**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The response to this epitope was not detected until month 25 and increased over time.

**HXB2 Location** RT (309–317)  
**Author Location** Pol  
**Epitope** ILKEPVHGV

**Epitope name** I9V

**Immunogen** vaccine

*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140 $\Delta$ V3

**Species (MHC)** transgenic mouse (A\*0201)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells

**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** RT (309–317)  
**Author Location** RT

**Epitope** ILKEPVHGV

**Epitope name** IV9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** HAART, ART, responses in children, dendritic cells

**References** Zhang *et al.* 2006

- Immune responses in HIV-1 infected children either undergoing HAART or not were analysed. HIV-specific CTLs were lower in children responding to HAART than in non-responders and HAART-naive children. CTL frequency was correlated with myeloid DC frequency in treatment-naive patients, and inversely correlated with duration of virus suppression following treatment.
- 11 of the 22 children had significant responses to SL9.

**HXB2 Location** RT (309–317)  
**Author Location** RT (476–484 LAI)  
**Epitope** ILKEPVHGV  
**Epitope name** P1  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*0205)  
**Keywords** HAART, ART  
**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using tetramer staining or CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** RT (309–317)  
**Author Location** RT (309–317)  
**Epitope** ILKEPVHGV  
**Epitope name** IV9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A02)  
**Assay type** Chromium-release assay, Other  
**Keywords** binding affinity  
**References** Bennett *et al.* 2007

- Standard assays like ELISpot, ICS and tetramer staining do not measure antiviral activity of HIV-infected CTLs, but use exogenous synthetic peptides on uninfected cells or HLA tetramers. Similarly, functional avidity assesses CTL activity against uninfected target cells. Here functional avidity is compared to the efficiency of actual infected cells' recognition and killing, revealing a sharp threshold between CTL immune antiviral activity and lack of infected cell recognition.
- As previously shown, epitopes and their variants spanned orders of magnitude of SD50. Likewise, CTL clearance of infected cells varied from 0 to 100% with epitope sequence variation. Moreover, direct suppression of HIV-1 replication by CTLs also varied with epitope variant.
- When killing efficiency (KE) using virus-infected cells was compared to functional avidity using synthetic peptides, there was a narrow threshold separating maximal killing from almost none. Since different SL9-specific clones had similar KEs, which were vastly different from RL10-specific CTL KEs, it was obvious that KEs varied with epitope sequence too. Finally, a strong correlation between KE and inhibition of viral replication was also seen.
- This epitope, ILKEPVHGV, showed marked differences in its functional avidity as well as killing efficiency, when compared to its variants ILKdPVHGV, ILKnPVHGV, ILKdPVHG<sub>a</sub>, ILKtPVHGV, ILrPVHGV, ILKEsVHGV, ILKEtVHGV, ILKEPVHG<sub>a</sub>, ILKEPVHeV, ILKqPVHGV, liKEPVHGV, ILrtPVHGV, ILKEPVHrV, ILKEPIHGV, kLKEPVHGV and ILKEIVHGV.

**HXB2 Location** RT (309–317)  
**Author Location**  
**Epitope** ILKEPVHGV  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

- Species (MHC)** human (A02)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells  
**References** Horton *et al.* 2006a
- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
  - B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** RT (309–317)  
**Author Location**  
**Epitope** ILKEPVHGV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A02)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity  
**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope ILKEPVHGV elicited a magnitude of response of 110 SFC with a functional avidity of 0.01nM.

**HXB2 Location** RT (309–317)  
**Author Location** Pol (476–484)  
**Epitope** ILKEPVHGV  
**Immunogen** vaccine  
*Vector/Type:* vaccinia  
**Species (MHC)** human (A2)  
**References** Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D<sup>d</sup> – this transgene is the only MHC molecule expressed in the mice.

- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccination boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWYCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFD-SRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- ILKEPVHGV was recognized by 2 of the patients.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons, TCR usage

**References** Kolowos *et al.* 1999

- TCR usage in CTL specific for this epitope was examined in three patients and identical V $\beta$ 6.1 and Valpha2.5 gene segments were used and two of the patients had very similar complementarity-determining regions – clonal expansion of RT-HIV-specific CTL can contribute to the skewed TCR repertoire in HIV-1 infected patients.
- CTL clones from all three patients showed similar sensitivity to mutation in the epitope, ilkepvhEv was well recognized (the sequence from SF2), ilkDpvhgv was not (the common A clade form)

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Collins *et al.* 1998

- Nef down-regulates MHC class I molecules, which inhibits CTL killing of HIV-infected targets.
- The anti-RT CTL clone killed Nef- cells less efficiently than anti-gag clones, correlated with the reduced expression of RT.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484 LAI)

**Epitope** ILKEPVHGV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** dendritic cells

**References** Fan *et al.* 1997

- The capacity of dendritic cells to process and present antigen and stimulate anti-HIV-1 CTL memory responses was studied.

**HXB2 Location** RT (309–317)

**Author Location** RT (464–472)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** dendritic cells

**References** Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.
- ILKEPVHGV is a conserved HLA-A2 epitope included in this study – 5/6 patients had this sequence as their HIV direct sequence, and these had a detectable CTL response – one person carried the form ILREPvhGV and had no detectable CTL.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Menendez-Arias *et al.* 1998; Tsomides *et al.* 1994

- CTL clones recognize naturally processed peptide – peptide abundance corresponded to level of CTL killing.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A2)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is ILKDPVHGV.
- The D subtype consensus is identical to the epitope ILKEPVHGV.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Cao *et al.* 1997a; Menendez-Arias *et al.* 1998

- The consensus peptides of B and D clade viruses and some A have the sequence ILKEPVHGV.
- The consensus peptide of a subset of A clade viruses, ILKD-PVHGV, is not cross-reactive.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**References** Menendez-Arias *et al.* 1998; Yang *et al.* 1996

- CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL.
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones.
- The distinction was thought to be due to lower expression of RT relative to Env and Gag.
- CTL can lyse infected cells early after infection, possibly prior to viral production.

**HXB2 Location** RT (309–317)**Author Location** RT (476–484)**Epitope** ILKEPVHGV**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Assay type** CTL suppression of replication**References** Yang *et al.* 1997a

- CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*.
- CTL produced HIV-1-suppressive soluble factors – MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, after antigen-specific activation.
- CTL suppress HIV replication more efficiently in HLA-matched cells.

**HXB2 Location** RT (309–317)**Author Location** RT (309–317)**Epitope** ILKEPVHGV**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Keywords** TCR usage**References** Menendez-Arias *et al.* 1998; Moss *et al.* 1995

- Two clones were obtained with different TCR usage, V $\beta$ 1 and V $\beta$ 21.

**HXB2 Location** RT (309–317)**Author Location** RT (476–484)**Epitope** ILKEPVHGV**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**References** Menendez-Arias *et al.* 1998; Musey *et al.* 1997

- Cervical CTL clones from an HIV-infected woman recognized this epitope.

**HXB2 Location** RT (309–317)**Author Location** RT (476–484 LAI)**Epitope** ILKEPVHGV**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**References** Menendez-Arias *et al.* 1998; Tsomides *et al.* 1991

- Precise identification of the nonamer that binds to A2.

**HXB2 Location** RT (309–317)**Author Location** RT (476–484 LAI)**Epitope** ILKEPVHGV**Subtype** B**Immunogen** peptide-HLA interaction**Species (MHC)** human (A2)**References** Connan *et al.* 1994; Menendez-Arias *et al.* 1998

- Promotes assembly of HLA-A2 molecules in T2 cell lysates.

**HXB2 Location** RT (309–317)**Author Location** RT (510–518)**Epitope** ILKEPVHGV**Immunogen** *in vitro* stimulation or selection**Species (MHC)** human (A2)**References** Parker *et al.* 1992

- Studied in the context of HLA-A2 peptide binding.

**HXB2 Location** RT (309–317)**Author Location** Pol (476–484)**Epitope** ILKEPVHGV**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**References** Dyer *et al.* 1999

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

**HXB2 Location** RT (309–317)**Author Location** RT (476–484)**Epitope** ILKEPVHGV**Immunogen** *in vitro* stimulation or selection**Species (MHC)** human (A2)**Keywords** dendritic cells**References** Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYK-TLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

**HXB2 Location** RT (309–317)**Author Location** RT (480–)**Epitope** ILKEPVHGV**Immunogen** computer prediction**Species (MHC)** (A2)**Keywords** subtype comparisons**References** Schafer *et al.* 1998

- This study uses EpiMatrix for T cell epitope prediction to identify possible HLA-B27 and A-2 CTL epitopes in HIV.



- Based on EpiMatrix predictions, 28 peptides were synthesized and tested using T2 binding assays for potential HLA A2 or B27 binding, and 12 of these were shown to bind to the predicted HLA molecule.
- Two of these 12 peptides had been previously identified as CTL epitopes: HLA-B27 KRWILGLNK and HLA-A2 ILKEPVHGV.
- This sequence is not conserved between clades, but is found only in a small number of B clade isolates.

**HXB2 Location** RT (309–317)

**Author Location** RT

**Epitope** ILKEPVHGV

**Epitope name** RT IV9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** binding affinity, subtype comparisons, super-type, computational epitope prediction

**References** Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- This peptide binds to four HLA-A2 supertype alleles: A\*0201, A\*0202, A\*0206 (highest affinity) and A\*6802.
- RT IV9 was recognized in 7/22 patients with chronic HIV-1 infection.
- 1/13 patients with acute HIV-1 infection recognized RT IV9.

**HXB2 Location** RT (309–317)

**Author Location** Pol (subtype A)

**Epitope** ILKDPVHGV

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HIV exposed persistently seronegative (HEPS), escape

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- ILKDPVHGV or ILKEPVHGV was recognized in 1 of the 6 women (ML1760), and the response was present in the last available sample prior to seroconversion, 12 months.
- 20/20 sequences of the infecting strain had no substitutions in this epitope, all were ILKDPVHGV, so there was no evidence for escape.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.

- This epitope was recognized by 4/22 HEPS control sex workers: ML887, ML1192, ML1250, and ML1749.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Epitope name** ILK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- One of the 2/8 HLA-A2+ study subjects recognized this CTL epitope.
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGGL, ILKEPVHGV, SQRRQDILDWYHTQGYFPDWQNY, and GEIYKRWII peptides and all responses declined during therapy initiated at day 390 but were restored when therapy became intermittent.

**HXB2 Location** RT (309–317)

**Author Location** Pol

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.

**HXB2 Location** RT (309–317)

**Author Location** Pol

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART, immunodominance

**References** Seth *et al.* 2001

- CTL responses were studied by tetramer staining in 41 patients with combination therapy – activated CD8+ T-cells decline as the viral load drops in response to therapy, but the overall level of antigen-specific cells capable of differentiating into effectors stays constant and new epitopes may be recognized.

- 6/10 A\*0201+ individuals had HIV-specific tetramer staining cells, and 5 of these declined upon successful therapy.
- 3/10 A\*0201+ individuals with chronic HIV-1 infection recognized this epitope.
- Prior to therapy, the mean percentage of CD8+ cells that recognized the immunodominant epitope SLYNTVATL was six-fold greater than the percentage recognizing the epitope ILKEPVHGV.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484 SF2)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 0/6 group 2, and 3/4 group 3.

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKDPVHGV

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A2)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- Variants ILK(D/E)PVHGV are A/B clade specific.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A2 women, 7/10 HEPS and 14/26 HIV-1 infected women recognized this epitope, and ILK(D/E)PVHGV tended to be more reactive in HEPS women, SL(F/Y)NTVATL in infected women.

- The dominant response to this HLA allele was to this epitope in all 7/10 HEPS cases but in only 5 of the 14/26 HIV-1 infected women.
- Four epitopes were considered to be “resistant epitopes”, as they were preferentially reactive in HEPS women and so may confer resistance, and these were found in three different proteins: A2 ILK(D/E)PVHGV in RT, A\*6802 DTVLEDINL in Protease, B14 DLN(M/T)LN(I/V)V in p24 and B18 FRDYV-DRF(Y/F)K also in p24.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A\*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Subject ML 1250 had an A2 response to ILK(D/E)PVHGV prior to seroconversion, which switched to SL(F/Y)NTVATL post-seroconversion.
- Subject ML 1760 had an A2 response to ILK(D/E)PVHGV prior to seroconversion, and gained responses to epitopes A2 SL(F/Y)NTVATL and B27 KRWII(L/M)GLNK post-seroconversion.

**HXB2 Location** RT (309–317)

**Author Location** Pol (93TH253 subtype CRF01)

**Epitope** ILRIPVHGV

**Epitope name** P464-472

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2.

**HXB2 Location** RT (309–317)

**Author Location** Pol (93TH253 subtype CRF01)

**Epitope** ILRIPVHGV

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by two amino acids: ILKEPVHGV.
- This epitope was not conserved in many subtypes, and exact matches were very rare.

- HXB2 Location** RT (309–317)  
**Author Location** RT (309–317)  
**Epitope** ILKEPVHGV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** rate of progression, acute/early infection  
**References** Day *et al.* 2001
- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
  - 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

- HXB2 Location** RT (309–317)  
**Author Location**  
**Epitope** ILKEPVHGV  
**Epitope name** Pol-IV9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Sabbaj *et al.* 2003
- Among HIV+ individuals who carried HLA A02, 9/29 (31%) recognized this epitope.

- HXB2 Location** RT (309–317)  
**Author Location** Pol (476–484 LAI)  
**Epitope** ILKEPVHGV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** HAART, ART, epitope processing  
**References** Kelleher *et al.* 2001a
- Ritonavir (RTV) inhibits chymotryptic activity in the 20S proteasome *in vitro*, as does Saquinavir (SQV) to a lesser extent; Indinavir (IDV) does not. Thus there is concern protease inhibitors may adversely effect CTL epitope processing, but this paper indicates that processing is not inhibited at therapeutically relevant concentrations of RTV when the proteasome is functioning in an intracellular context.
  - RTV did not alter the presentation two RT A2 epitopes processed by distinct pathways: ILKEPVHGV, generated by the constitutive proteasome containing the MB1 beta subunit, and VIYQYMDDL which is dependent on IFN $\gamma$  induction of LMP7 which replaces MB1 in the immunoproteasome, and is destroyed by MB1 in the constitutive proteasome.
  - RTV did not inhibit the processing and assembly of HLA-B35 or -A2, which are assembled with a rapid and moderate time course, respectively, or of HLA-A3, -B27 and -B39.

- HXB2 Location** RT (309–317)  
**Author Location** Pol  
**Epitope** ILKDPVHGV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** HIV exposed persistently seronegative (HEPS)

- References** Kaul *et al.* 2002
- Neisseria gonorrhoea cervicitis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN- $\gamma$  production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
  - Ghonorrhoea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN- $\gamma$  production.

- HXB2 Location** RT (309–317)  
**Author Location** RT (476–484 NL43)  
**Epitope** ILKEPVHGV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** class I down-regulation by Nef  
**References** Yang *et al.* 2002
- Nef down-modulates class I protein expression, and this study demonstrates directly that Nef-deleted HIV-1 NL-43 can be more effectively killed *in vitro* than NL-43 with an intact Nef. The effect was shown to be specific for class I presentation of epitopes, and unlike Nef, deleting Vpr did not alter CTL susceptibility of NL-43 infected cells. The CTL clone 68A62, specific for the class I A2 presented ILKEPVHGV epitope, was one of four used in this study.

- HXB2 Location** RT (309–317)  
**Author Location** RT (476–484 BRU)  
**Epitope** ILKEPVHGV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A2  
**Keywords** epitope processing  
**References** Cohen *et al.* 2002
- The antigen presentation of two A2-restricted epitopes was compared, SLYNTVATL (p17) and ILKEPVHGV (RT). HIV-1 infected cells were more sensitive to lysis by SLYNTVATL-specific CTL than by ILKEPVHGV-specific CTL, because of a higher density of SLYNTVATL-A2 resulting from differences in processing.
  - Incubation with a T1-cell proteolytic extract showed that by four hours, 25% of a p17 peptide had a C-term Leu-85 and were SLYNTVATL-precursors, while ILKEPVHGV-precursors were far less frequent (6.8%) even with four times more proteolytic extract after 30 hours.
  - p17 was preferentially cleaved between Leu85 and Tyr86, while appropriate Val484 and Tyr485 cleavage was minor for RT.
  - In a competition experiment, RSLYNTVATL bound TAP 3.7-fold more efficiently than RT peptides.
  - No difference in CTL avidity was detected in six patients with HLA-A2-restricted responses to these epitopes.
  - No significant difference in HLA-A2 binding of to p17 or RT epitopes was observed.

- HXB2 Location** RT (309–317)  
**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV**Epitope name** p9**Immunogen** vaccine*Vector/Type:* peptide *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (A2)**References** De Lucca *et al.* 2002

- BALB/c mice immunized with the p9 peptide, ILKEPVHGV, elicited specific lymphocyte proliferation activity.
- Exposure of lymphocytes from HIV-negative, HLA-A2 positive people to p9-RNA stimulated lymphocyte proliferation activity to p9. Anti-p9 CTL activity in human lymphocytes incubated with RNA extracted from lymphoid organs of p9-vaccinated mice could be more intensely stimulated.
- This murine RNA also mediated RNA-dependent protein kinase (PKR) and NFkappaB activation in the human lymphocytes, which may be driving the enhanced CTL stimulation in the human cells.

**HXB2 Location** RT (309–317)**Author Location** RT**Epitope** ILKEPVHGV**Epitope name** ILK**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Keywords** HAART, ART, supervised treatment interruptions (STI)**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFNgamma Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** RT (309–317)**Author Location** p51 (476–484)**Epitope** ILKEPVHGV**Immunogen** vaccine*Strain:* B clade IIIB *HIV component:* Gag, Pol *Adjuvant:* IL-12**Species (MHC)** mouse (A2)**Donor MHC** H2-K<sup>b</sup>**References** Kmiecik *et al.* 2001

- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with either a p17-p24-p51 fusion protein (vG/P-92) or the Gag-Pol precursor protein (vVK1).
- Compared to vVK1, vG/P-92 induced a significant increase in Gag and Pol induced IFNgamma production and CTL responses, and to the epitopes SLYNTVATL and ILKEPVHGV, as determined by Elispot and 51Cr-release assays.

**HXB2 Location** RT (309–317)**Author Location** RT (309–317 NL-43)**Epitope** ILKEPVHGV**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Keywords** class I down-regulation by Nef, escape**References** Ali *et al.* 2003

- NL43 was passaged in the presence of Nef KEKGGLEGL-specific CTL clones STD11 and KM3, giving rise to rapid selection of escape mutations, including E93G, E93K, K94N+G99R, G95R+G99R, E98K, E98D, G99R, G99E, L100P, and L100I; insertions, deletions, frameshifts and an early stop codon. 34/36 (94%) of sequences carried mutations in the epitope by seven days, 36/36 (100%) by 14 days.
- Several mutations selected by KEKGGLEGL-specific CTL were shown to impair the down regulation of class I MHC by Nef, in particular E93G, E93K, and a truncation mutation at position 51.
- Nef deletion mutants increased 100-fold NL-43 susceptibility to inhibition by CTL specific for epitopes in other proteins, the A2 epitopes ILKEPVHGV in RT and SLYNTVATL in p17 Gag.

**HXB2 Location** RT (309–317)**Author Location** Pol (476–)**Epitope** ILKEPVHGV**Epitope name** Pol476**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** binding affinity, subtype comparisons, computational epitope prediction**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- 9/17 HIV-infected HLA-A2+ people recognized this epitope.

**HXB2 Location** RT (309–317)**Author Location** RT (309–317)**Epitope** ILKEPVHGV**Epitope name** RT2**Subtype** B**Immunogen** vaccine, in vitro stimulation or selection*Vector/Type:* peptide *HIV component:* RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)**Species (MHC)** transgenic mouse (A2)**References** Domingo *et al.* 2003

- A virus-like protein scaffold, called E2DISP, derived from pyruvate dehydrogenase multienzyme from *Bacillus stearothermophilus* has been engineered to display 60 copies of one or more epitopes on a single molecule.
- The E2DISP scaffold displaying pep23 is able to stimulate a Th responses, and peptide RT2, which is a CTL epitope from HIV-1 RT, was able to elicit a CD8+ T cell response *in vitro* and in a vaccinated HLA-A2 transgenic mouse. Thus the E2DISP scaffold allows cell-entry and access to the class I and class II processing pathways.

- HXB2 Location** RT (309–317)  
**Author Location** Pol (476–484)  
**Epitope** ILKEPVHGV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Flow cytometric T-cell cytokine assay  
**Keywords** responses in children  
**References** Sandberg *et al.* 2003
- 65 vertically HIV-1 infected children, ages 1-16, the majority undergoing ART, were analyzed in regard to their plasma viremia and CD4+ and CD8+ T cell counts, and CD8+ T cell responses.
  - Using vaccinia expressed Gag, Pol, Env, Rev, Nef in target cells in an Elispot assay, 85% of the children recognized at least one HIV antigen. The strong CD8+ T cell responses were directed against Pol, followed by Gag and Nef. Children younger than 4 had significantly weaker responses (7/14 had no response) than older children (only 1/32 had no response, and responses were greater in magnitude).
  - SLYNTVATL and ILKEPVHGV tetramers were used to quantify specific responses. 49 children in an expanded cohort carried HLA-A2. 1/11 children under 3 years of age had detectable CD8+ T-cell responses to SLYNTVATL, 2/11 to ILKEPVHGV. Among children over 3, 11/38 recognized SLYNTVATL and 9/38 recognized ILKEPVHGV.
  - Older children that maintained a CD4 count greater than 400 cells/ul tended to have stronger CTL responses.

- HXB2 Location** RT (309–317)  
**Author Location** RT (309–317)  
**Epitope** ILKEPVHGV  
**Immunogen** HIV-1 infection  
**Species (MHC)** (A2)  
**Donor MHC** A2, A3, B27, B51; A2, A3, B27, B57; A2, A23, B57  
**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining  
**Keywords** assay standardization/improvement, memory cells  
**References** Sun *et al.* 2003
- This study compares assay methods for testing CTL responses using samples from 20 HIV+ patients. The study compares ELISpot, tetramer-binding, and intracellular IFN- $\gamma$ . Tetramer-binding analysis was performed with Gag (SLYNTVATL) or Pol (ILKEPVHGV) tetramers. Antigen presentation using recombinant vaccinia viruses (rVVs) encoding HIV-LAI Gag, Pol, Env, Nef, Tat and Vif proteins was compared to peptide panels. HIV antigen recognition in memory CTLs was measured by chromium release assay and compared to effector/memory CD8+ T cells in an IFN- $\gamma$  ELISpot assay.
  - Results: IFN- $\gamma$  Elispot and flow cytometry gave similar frequencies of HIV specific CD8+ T cells. Tetramer-binding analysis was most sensitive. Pools of peptides and the sum of frequencies of individual peptides were comparable. Elispot assays using peptides were more sensitive than assays using vaccinia expressed proteins. Cr release and Elispot against rVVs gave comparable memory cell responses 2/3s of the time.

- 3/7 HLA-A2+ patients recognized this epitope.

- HXB2 Location** RT (309–317)  
**Author Location** RT (309–317 NL43)  
**Epitope** ILKEPVHGV  
**Epitope name** IV9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Assay type** Chromium-release assay, CTL suppression of replication  
**Keywords** escape  
**References** Yang *et al.* 2003a
- Virus was cultured in the presence of CTL lines specific for 4 different epitopes (SLYNTVATL, ILKEPVHGV, IEIKDTKEAL, and KEKGGLEGL) to study the emergence of escape mutations. Escape varied between clones for the same epitope, and between different epitopes. Gag and RT epitope escape, if it occurred at all, tended to be monoclonal and within the epitope, indicating strong fitness constraints, while the Nef epitope escape was rapid, polyclonal, and sometimes the result of upstream frameshifts.
  - There was one cloned cell line that recognized ILKEPVHGV, 68A62. After 2 weeks of passaging HIV-1 in the presence of 68A62, the mutated epitope ilkeLvghv was found in 6/12 sequences.

- HXB2 Location** RT (309–317)  
**Author Location** Pol  
**Epitope** ILKEPVHGV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Koning *et al.* 2004
- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
  - 2/11 HLA A2+ infection-resistant men, compared to 1/9 pre-seroconversion men who went on to become infected, reacted to this epitope.

- HXB2 Location** RT (309–317)  
**Author Location** RT Pol (464–472)  
**Epitope** ILKEPVHGV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 9/19 patients recognized this epitope.

**HXB2 Location** RT (309–317)

**Author Location** RT (309–317)

**Epitope** ILKEPVHGV

**Epitope name** RT-IV9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** Chromium-release assay

**Keywords** binding affinity, TCR usage, characterizing CD8+ T cells

**References** Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 2/14 CTL T-cell clones tested were specific for RT/IV9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 values for the two RT/IV9 clones were very different, 50 and 20,000 pg/ml.

**HXB2 Location** RT (309–317)

**Author Location** (B consensus)

**Epitope** ILKEPVHGV

**Epitope name** IV9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A02, A03, B08, B62, Cw10, Cw7

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** RT (309–317)

**Author Location** RT (309–317)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** Chromium-release assay

**Keywords** assay standardization/improvement

**References** Lubong *et al.* 2004

- Using IL7 or IL15 in culturing of HIV-1-specific CTL clones was inferior to using IL-2 alone; the addition of these cytokines to IL-2 did not show any advantage. Neither proliferation, survival, nor lytic capacity of HIV-1-specific CTLs was significantly enhanced by addition of IL7 or IL15.

**HXB2 Location** RT (309–317)

**Author Location** Pol

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A2)

**Donor MHC** A\*02, A\*30, B\*15, B\*4402

**Assay type** Tetramer binding, T-cell Elispot

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.
- This patient responded to 4/8 HIV epitopes tested in an IFN-gamma EliSpot assay or tetramer assay. Responses were detected 8 and 28 weeks after exposure. A response to ILKEPVHGV was detected by both assays.

**HXB2 Location** RT (309–317)

**Author Location** Pol

**Epitope** ILKEPVHGV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United Kingdom

**Assay type** Tetramer binding, T-cell Elispot, Intracellular cytokine staining

**Keywords** rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction

**References** Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

**HXB2 Location** RT (309–317)

**Author Location** (309–317)

**Epitope** ILKEPVHGV

- Epitope name** RT2  
**Immunogen** vaccine  
*Vector/Type:* bacteriophage coat protein, dihydrolipoyl acetyltransferase E2 protein, of *Bacillus stearothermophilus* HIV component: RT
- Species (MHC)** transgenic mouse (A2)  
**Assay type** Chromium-release assay  
**Keywords** vaccine antigen design  
**References** De Berardinis *et al.* 2003
- An RT T-helper (KDSWTVNDIQKLVGK) that can be promiscuously presented by multiple HLA-DR molecules, and an RT CTL epitope (ILKEPVHGV) presented by HLA-A2, were displayed using two different antigen presentation systems, bacteriophage virions or E2 protein scaffolds. Both systems enabled display of the epitopes in a mouse model system to the immune system. CTL responses were detected in immunized mice, and were processed correctly for both class I and class II presentation.
- HXB2 Location** RT (309–317)  
**Author Location** Pol  
**Epitope** ILKEPVHGV  
**Epitope name** IV9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a
  - Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - Two escape mutations, at positions 3 ilRepvhg, and 9 ilkepvhgA, were found not to correspond to the most polymorphic residues in the epitope.

**HXB2 Location** RT (309–317)  
**Author Location** RT (309–317)  
**Epitope** ILKEPVHGV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding  
**Keywords** acute/early infection, optimal epitope  
**References** Altfeld *et al.* 2005
  - The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection.
  - ILKEPVHGV was targeted in 54% of 74 A2+ chronically infected individuals, but only 1/14 acutely infected A2+ individuals.

**HXB2 Location** RT (309–317)

- Author Location**  
**Epitope** ILKEPVHGV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** Germany  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, escape, variant cross-recognition or cross-neutralization, optimal epitope  
**References** Harrer *et al.* 2005
- An HLA-B13-restricted optimal epitope was defined in Nef, RI9. The frequency of CTLs specific for this epitope in B13-positive patients exceeded the number of CTLs against other epitopes, indicating that this is a dominant epitope in B13-positive subjects. Three B13-positive patients who had an immunodominant response to this epitope were good controllers of their infection, with low viral loads over long periods.
  - 5 HLA A2+ B13+ patients were found to make an immunodominant response to the B13 epitope RI9. 0/5 recognized the A2 epitope ILKEPVHGV, and only 1/5 recognized the A2 epitope SLYNTAVTL, with a much lower frequency than the B13 response.
- HXB2 Location** RT (309–317)  
**Author Location** Pol (476–484 BRU)  
**Epitope** ILKEPVHGV  
**Subtype** B, CRF02\_AG  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** Cote D'Ivoire  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons  
**References** Inwoley *et al.* 2005
  - CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
  - This epitope was recognized by 2/9 CRF02\_AG-infected Ivoirians, and 1/9 B-infected French subjects.

**HXB2 Location** RT (309–317)  
**Author Location** RT (77–85)  
**Epitope** ILKEPVHGV  
**Epitope name** IL9  
**Subtype** B  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (A2)  
**Country** Canada  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance, genital and mucosal immunity, characterizing CD8+ T cells  
**References** Makedonas *et al.* 2005
  - CD8 T-cell responses were studied in individuals who remained seronegative in spite of being mucosally (group 1) or intravenously (group 2) exposed to HIV-1. A similar proportion of subjects from each group recognized at least 1 HIV peptide, and they recognized peptides with similar cumulative

intensity. The proportion of responding individuals in both groups was significantly greater than in a low-risk, negative control group. One exposed uninfected subject recognized 7 epitopes.

- HLA-A\*0201 epitopes that are immunodominant in chronically infected individuals were rarely stimulatory in exposed uninfected individuals. SLYNTVATL was recognized by one HLA A2+ individual in each group (1/11 vs 1/5), while none of the exposed uninfected individuals tested responded to ILKEPVHGV. In contrast, chronically infected subjects recognized these epitopes at a frequency of 69% and 31%, respectively.

**HXB2 Location** RT (309–317)

**Author Location** RT (476–484)

**Epitope** ILKEPVHGV

**Epitope name** IV9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Germany

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** HAART, ART, TCR usage, characterizing CD8+ T cells, optimal epitope

**References** Schmitt-Haendle *et al.* 2005

- CTL responses to 3 HLA-A2-restricted epitopes were investigated in 51 HIV-1 infected HLA-A2+ individuals. The most prevalent response was seen for IV9, followed by SL9. The VL9 epitope was not recognized. There was a significant correlation of CTL activity to the CD8 counts in peripheral blood, but no correlation to CD4 counts, viral load, or antiviral therapy.
- 37.3% of the individuals recognized ILKEPVHGV.
- All analyzed mutations for RT-IV9 epitope could decrease or abrogate CTL recognition dependent on the CTL clones tested, but all were fully immunogenic for other CTL clones. The ilkDpvhgv, ilkepvhEv, Rlkepvhgv and ilRepvhgv variants were tested.

**HXB2 Location** RT (309–317)

**Author Location** RT

**Epitope** ILKEPVHGV

**Epitope name** A2-IV9(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (309–317)

**Author Location**

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining

**Keywords** responses in children, rate of progression

**References** Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking attribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Response detected in 1 LTNP child and 1 early non-progressive child.

**HXB2 Location** RT (309–317)

**Author Location** Pol (476–484)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

**HXB2 Location** RT (309–317)

**Author Location** Pol (464–472)

**Epitope** ILKEPVHGV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A2)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** RT (309–317)

**Author Location** Pol (subtype B)

**Epitope** ILKEPVHGV



**Subtype B****Immunogen** HIV-1 exposed seronegative**Species (MHC)** human (A\*0202, A2)**Keywords** subtype comparisons**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- Clade A version of the epitope, ILKDPVHGV, was preferentially recognized by CTL.

**HXB2 Location** RT (309–317)**Author Location** RT (309–317)**Epitope** ILKEPVHGV**Epitope name** RT2**Immunogen** vaccine, *in vitro* stimulation or selection*Vector/Type:* HIV-1 peptide in filamentous bacteriophage major coat protein *HIV component:* RT**Species (MHC)** human, mouse (A2, A2 transgenic)**Keywords** epitope processing**References** De Berardinis *et al.* 2000

- Phage display of the CTL epitope, ILKEPVHGV coupled with T helper epitope KDSWTVNDIQKLVGK, elicited specific CTL responses *in vitro* in PBMC from HIV negative individuals in and *in vivo* in immunization of HLA-A2 transgenic mice.
- Bacteriophage presentation of peptides is generally used for stimulation of antibodies, and this novel discovery of CTL epitope processing and presentation suggests new possibilities for these vectors.

**HXB2 Location** RT (309–317)**Author Location** RT (476–484 LAI)**Epitope** ILKEPVHGV**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A\*0201**Keywords** HAART, ART, responses in children**References** Luzuriaga *et al.* 2000

- Longitudinal study of 8 infants with prolonged viral suppression due to combination antiretroviral therapy showed no HIV-1 specific CTL responses in peripheral blood cells. 6/8 were studied using a Chromium release assay and no response was detected using Gag expressed in vaccinia in the target cells. Three HLA-A\*0201 children were tested using SLYNT-VATL or ILKEPVHGV HLA A\*0201 tetramers and again no HIV-specific response was detected, either using PBMC specimens, or PBMC which had been stimulated *in vitro* for a week.
- In contrast, one of the children with suppressed HIV viral replication who was co-infected with HIV and EBV, while HIV-tetramer negative, had EBV-tetramer staining cells at a frequency of 0.14% in the PBMC.

**HXB2 Location** RT (309–317)**Author Location****Epitope** ILKEPVHGV**Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other**Keywords** binding affinity, acute/early infection**References** Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127<sup>lo</sup>, CD38<sup>+</sup>, Ki-67<sup>hi</sup> CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope ILKEPVHGV seen in 1 patient, underwent sequence changes.

**HXB2 Location** RT (309–318)**Author Location** Pol**Epitope** ILKEPVHGVY**Epitope name** 1249**Subtype** multiple**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Donor MHC** A02, A30, B39; A02, A03, B44, Cw05, Cw07; A02, A30, B35, B49, Cw04, Cw07**Country** United States**Assay type** T-cell Elispot**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for ILKEPVHGVY: 96% Promiscuous epitope binding to A02 and Bw62.

**HXB2 Location** RT (309–318)**Author Location** RT (476–485 LAI)**Epitope** ILKEPVHGVY**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*1501)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1501 epitope.

**HXB2 Location** RT (309–318)**Author Location** RT (309–317)

**Epitope** ILKEPVHGVY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B15)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, escape  
**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** RT (309–318)

**Author Location** RT

**Epitope** IKLEPVHGVY

**Epitope name** B15-IY10(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (309–318)

**Author Location** RT (476–485 LAI)

**Epitope** ILKEPVHGVY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** review

**References** McMichael & Walker 1994; Menendez-Arias *et al.* 1998

- Review of HIV CTL epitopes.

**HXB2 Location** RT (309–318)

**Author Location** RT (309–318)

**Epitope** IKLEPVHGVY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** immunodominance

**References** Day *et al.* 2001

- No immunodominant responses were detected to four B62-restricted epitopes tested.

**HXB2 Location** RT (309–318)

**Author Location** Pol

**Epitope** ILKEPVHGVY

**Subtype** A, B, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade HIV component: p17 Gag, p24 Gag

**Species (MHC)** human (B62)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** RT (317–325)

**Author Location** Pol (484–492)

**Epitope** VYDPSKDL

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance, characterizing CD8+ T cells

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 1/9 CRF02\_AG-infected Ivoirians, and 0/9 B-infected French subjects.

- HXB2 Location** RT (317–326)  
**Author Location** RT Pol  
**Epitope** VYYDPSKDLI  
**Epitope name** RT2  
**Subtype** A, B, C  
**Immunogen** vaccine  
*Vector/Type:* DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT
- Species (MHC)** mouse (H-2K<sup>d</sup>)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism
- References** Larke *et al.* 2007
- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.
  - After immunization with any clade vaccine, index epitope RT2, VYYDPSKDLI, was recognized, as well as 2 variants at >70% levels, viz. VYYDPSKDLv and VYYDPtKDLI. Variants VYYDPSKeLI, aYYDPSKeLI, VYYePSKeLI were not recognized.
- HXB2 Location** RT (328–352)  
**Author Location** RT (495–515 LAI)  
**Epitope** EIQQGQGQWYQIYQEPFKNLKTG  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**References** Menendez-Arias *et al.* 1998; Walker *et al.* 1989
- One of five epitopes defined for RT-specific CTL clones in this study.
- HXB2 Location** RT (330–344)  
**Author Location**  
**Epitope** QKQGQGQWYQIYQE  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41
- Species (MHC)** human  
**Donor MHC** A\*2501, A\*3002; B\*0702, B\*1801  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes  
**References** Horton *et al.* 2006b
- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.

- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

- HXB2 Location** RT (333–341)  
**Author Location** Pol (488–496)  
**Epitope** GQGQWYQI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*13)  
**Donor MHC** A\*0301, A\*3001, B\*1301, B\*1402, Cw\*0602, Cw\*0802  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism
- References** Honeyborne *et al.* 2007
- To determine whether HLA-B\*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B\*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B\*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.

- HXB2 Location** RT (333–341)  
**Author Location**  
**Epitope** GQGQWYQI  
**Epitope name** GI9  
**Immunogen**  
**Species (MHC)** human (B13)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is a B13 epitope.

- HXB2 Location** RT (340–350)  
**Author Location** Pol (487–497 93TH253 subtype CRF01)  
**Epitope** QIYQEPFKNLK  
**Epitope name** P495-505  
**Subtype** CRF01\_AE  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (A11)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Sriwanthana *et al.* 2001
- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.

- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 128 who was HLA A11/A33.
- This epitope was reactive in HIV+ study subjects 053 and 184 who carried HLA-A11.

**HXB2 Location** RT (340–350)  
**Author Location** Pol (487–497 93TH253 subtype CRF01)  
**Epitope** QIYQEPFKNLK  
**Subtype** CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Keywords** subtype comparisons  
**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was not predicted by the EpiMatrix method to be likely to bind to A11, though it served as an epitope in the FSWs, and it was one of the six A11 epitopes that had been previously defined.
- 5/8 tested FSWs recognized this epitope.
- This epitope was highly conserved in other subtypes, although exact matches were not very common.

**HXB2 Location** RT (340–350)  
**Author Location** RT (507–516)  
**Epitope** QIYQEPFKNLK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Menendez-Arias *et al.* 1998; Price *et al.* 1995  
 • Study of cytokines released by HIV-1 specific activated CTL.

**HXB2 Location** RT (340–352)  
**Author Location** RT (507–519 LAI)  
**Epitope** QIYQEPFKNLKTG  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Keywords** review  
**References** Johnson & Walker 1994; Menendez-Arias *et al.* 1998

- This epitope was listed in a review.

**HXB2 Location** RT (340–352)  
**Author Location** Pol (495–507)  
**Epitope** QIYQEPFKNLKTG  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** RT (341–349)  
**Author Location** (C consensus)  
**Epitope** IYQEPFKNL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2301)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** RT (341–349)  
**Author Location** (C consensus)  
**Epitope** IYQEPFKNL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2301)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- IYQEPFKNL is an optimal epitope for both A\*2301 and A\*2402.

**HXB2 Location** RT (341–349)  
**Author Location** (C consensus)  
**Epitope** IYQEPFKNL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2402)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- IYQEPFKNL is an optimal epitope for both A\*2301 and A\*2402.

**HXB2 Location** RT (341–350)

**Author Location** RT (508–516)

**Epitope** IYQEPFKNLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**References** Culmann 1998

- C. Brander notes that this is an A\*1101 epitope in the 1999 database.

**HXB2 Location** RT (341–350)

**Author Location** RT (508–517 LAI)

**Epitope** IYQEPFKNLK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*1101 epitope.

**HXB2 Location** RT (341–350)

**Author Location** (C consensus)

**Epitope** IYQEPFKNLK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- IYQEPFKNLK is an optimal epitope.

**HXB2 Location** RT (341–350)

**Author Location** RT (508–517 SF2)

**Epitope** IYQEPFKNLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.

- Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 1/2 group 3.

**HXB2 Location** RT (341–350)

**Author Location** Pol (508–516)

**Epitope** IYQEPFKNLK

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** RT (341–350)

**Author Location** Pol (497–506)

**Epitope** IYQEPFKNLK

**Epitope name** IK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** optimal epitope

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

**HXB2 Location** RT (341–350)

**Author Location** Pol (497–506)

**Epitope** IYQEPFKNLK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** RT (346–354)

**Author Location** Pol (501–508)

**Epitope** FKNLKTGKY

**Subtype** B

**Immunogen** HIV-1 infection, peptide-HLA interaction

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** immunodominance

**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, FKNLKTGKY, is similar to human protein Str Spe Recognition protein, sequence FKNsKTG.

**HXB2 Location** RT (349–366)

**Author Location** (C consensus)

**Epitope** LKTGKYAKMRTAHTNDVK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0602)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (356–365)

**Author Location**

**Epitope** RMRGAHTNDV

**Epitope name** Pol-RV10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Donor MHC** A\*2904, A\*3002, B\*1503, B\*5802, Cw\*0202, Cw\*0602

**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.

- Subject 01RCH50 also recognized the epitope WRFDSRLAF, Nef(183–191), B\*1503.
- Among HIV+ individuals who carried HLA A30, 5/16 (31%) recognized this epitope.

**HXB2 Location** RT (356–365)

**Author Location** RT (356–365)

**Epitope** RMRGAHTNDV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** RT (356–366)

**Author Location** RT (356–366)

**Epitope** RMRGAHTNDVK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** RT (356–366)

**Author Location** RT (15–26)

**Epitope** RMRGAHTNDVK

**Epitope name** A3-RK11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 5/7 individuals began to have detectable responses to this epitope after STI.

**HXB2 Location** RT (356–366)

**Author Location** RT (356–366)

**Epitope** RTRGAHTNDVK

**Epitope name** A3-RK11 Pol

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant rtgahtndvR. The CTL response to both variants declined over time, and the response to the second variant was lower than to the first throughout.

**HXB2 Location** RT (356–366)

**Author Location** (B consensus)

**Epitope** RMRGAHTNDVK

**Epitope name** RK11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A02, A03, B08, B62, Cw10, Cw7

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** RT (356–366)

**Author Location** Pol (512–522)

**Epitope** RMRGAHTNDVK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** RT (356–366)

**Author Location** RT

**Epitope** RMRGAHTNDVK

**Epitope name** A3-RK11(RT)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (364–372)

**Author Location** RT (518–526 U455)

**Epitope** DVKQLTEVV

**Immunogen**

**Species (MHC)** human (A\*6802, A28)

**Keywords** subtype comparisons

**References** Dong 1998; Menendez-Arias *et al.* 1998

- Predicted on binding motif, no truncations analyzed.
- Reacts with clade A consensus (U455), and with the peptide DVKQLAEAV, from the D clade.

**HXB2 Location** RT (364–372)

**Author Location** RT (470–478 subtype A)

**Epitope** DVKQLTEVV

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human (B70)

**Keywords** subtype comparisons

**References** Dorrell *et al.* 1999

- CTL responses in three individuals with non-clade B infections were studied, 2 with subtype A infections, 1 with subtype C – their infections all originated in East Africa.
- This CTL response was defined in a patient with an A subtype infection.
- Bulk cultures from this patient gave a CTL response that could recognize the subtype D form of this epitope, with two substitutions (DVKQLAEAV), though a CTL line from these cultures didn't recognize the B clade variant (DVKQLTEAV)

**HXB2 Location** RT (366–385)

**Author Location** Pol (521–540)

**Epitope** KQLTEAVOKIAMESIVIWGK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.

- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** RT (373–390)

**Author Location** RT (373–390 HXB2)

**Epitope** QKIATESIWIWGKTPKFK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 21% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** RT (373–390)

**Author Location** Pol

**Epitope** QKIATESIWIWGKTPKFK

**Epitope name** POL-72

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.

- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187–2200 (2004)].
- This peptide, QKIAtESIWIWGKTPKFK differs from the consensus C sequence QKIAmESIWIWGKTPKFKr at 2 amino acid positions, i.e. by 10.5%.

**HXB2 Location** RT (373–390)

**Author Location** RT

**Epitope** QKIATESIWIWGKTPKFK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757–68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, QKIATESIWIWGKTPKFK, had an overall frequency of recognition of 16% - 22% AA, 15.4% C, 9.1% H, 14.3% WI.

**HXB2 Location** RT (374–383)



**Author Location****Epitope** KITTESIVIW**Epitope name** KW10**Immunogen** HIV-1 infection**Species (MHC)** human (B\*57)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B\*57-restricted optimal epitope KITTESIVIW was tested for immune response.

**HXB2 Location** RT (374–383)**Author Location** RT (374–383)**Epitope** KIATESIVIW**Epitope name** KW10**Immunogen** HIV-1 infection**Species (MHC)** human (B\*57)**Assay type** CTL suppression of replication**Keywords** class I down-regulation by Nef**References** Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein RT epitope KIATESIVIW-recognizing CTLs were affected by Nef.

**HXB2 Location** RT (374–383)**Author Location** RT**Epitope** KITTESIVIW**Epitope name** rtKW9**Immunogen** HIV-1 infection**Species (MHC)** human (B\*57)**Country** United Kingdom, Kenya**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** TCR usage, structure, characterizing CD8+ T cells**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFN-PEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** RT (374–383)**Author Location** RT (LAI)**Epitope** KITTESIVIW**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701)**Keywords** rate of progression**References** Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Patients studied were from the Amsterdam cohort.
- CTL epitopes of 3 rapid progressors were compared to 4 long-term survivors (LTS); no differences could be found in the degree of conservation between them.
- Epitope recognized by LTS and by a progressor.

**HXB2 Location** RT (374–383)**Author Location** RT (LAI)**Epitope** KITTESIVIW**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701)**References** van der Burg *et al.* 1997

- Recognized by CTL from a progressor and a long-term survivor, PIVLPEKDSW was also recognized.

**HXB2 Location** RT (374–383)**Author Location** RT Pol (529–538)**Epitope** KITTESIVIW**Immunogen** HIV-1 infection**Species (MHC)** human (B57)**Country** Spain**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

**HXB2 Location** RT (375–383)**Author Location** RT (375–383 LAI)**Epitope** ITTESIVIW**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (B\*5701, B\*5801)**Keywords** rate of progression**References** Klein *et al.* 1998

- Another patient recognized the ten-mer version of this epitope, KITTESIVIW van der Burg *et al.* [1997]
- B57 has been associated with long-term non-progression in the Amsterdam cohort.
- The most pronounced CTL responses in HLA B\*5701 LTS were to RT and Gag.
- The patient that recognized ITTESIVIW also recognized IVLPEKDSW.

**HXB2 Location** RT (375–383)**Author Location** (C consensus)

- Epitope** IAMESIVIW  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5703)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - IAMESIVIW is an optimal epitope for both B\*5801 and B\*5703
- HXB2 Location** RT (375–383)  
**Author Location** RT (375–383)  
**Epitope** IAMESIVIW  
**Immunogen**  
**Species (MHC)** human (B\*5801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- HXB2 Location** RT (375–383)  
**Author Location** (C consensus)  
**Epitope** IAMESIVIW  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - Mutational patterns in the S5 residue of IAMESIVIW are associated with the presence of the HLA presenting molecule in the host.
  - IAMESIVIW is an optimal epitope for both B\*5801 and B\*5703
- HXB2 Location** RT (375–383)  
**Author Location** (C consensus)  
**Epitope** IAMESIVIW  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*57, B\*5801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** RT (375–383)  
**Author Location** RT (375–383 SF2)  
**Epitope** ITTESIVIW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B57+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/2 group 3.

**HXB2 Location** RT (392–401)  
**Author Location** RT (559–568 LAI)  
**Epitope** PIQKETWETW  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (A\*3201)  
**References** Harrer *et al.* 1996b; Menendez-Arias *et al.* 1998

- Reviewed in Menendez-Arias *et al.* [1998], suggest the epitope is HLA B53/Cw2.
- C. Brander notes that this is an A\*3201 epitope in the 1999 database.

**HXB2 Location** RT (392–401)  
**Author Location** RT (559–568 LAI)  
**Epitope** PIQKETWETW  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (A\*3201)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*3201 epitope.

**HXB2 Location** RT (392–401)

**Author Location**

**Epitope** PIQKETWETW

**Epitope name** Pol-PW10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3201)

**Donor MHC** 01RCH59: A\*0201, A\*3201, B\*4002, B\*5301, Cw\*0202, Cw\*0401

**Keywords** HAART, ART

**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previous.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated.
- Subject 01RCH59 was Hispanic, was not on HAART, viral load 5100, CD4 count 349, and she also recognized QASQEVKNW, p24(176-184), B\*5301.
- Among HIV+ individuals who carried HLA A32, 1/2 (50%) recognized this epitope.

**HXB2 Location** RT (392–401)

**Author Location** RT (559–568 SF2)

**Epitope** PIQKETWETW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A32)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A32+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 1/1 group 2, and 0/0 group 3.

**HXB2 Location** RT (392–401)

**Author Location** RT

**Epitope** PIQKETWETW

**Epitope name** A32-PW10(RT)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A32)

**Donor MHC** A32, B14, B7; A32, B44; A30, A32, B18, B27

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient A displayed the greatest response to epitope B14-EL9(gp41), a strong response to B7-TL9(p24), and responses to B7-TM9(Nef) and A32-PW10(RT). Patient B displayed the greatest response to epitope B44-AW11(p24) and also responded to A32-PW10(RT) in both PB and LN samples, while a third response against epitope A32-RW10(gp120) was only detected in the LN sample. Patient D displayed the greatest response to B27-KK10 (p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

**HXB2 Location** RT (392–401)

**Author Location**

**Epitope** PIQKETWETW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A32)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope PIQKETWETW elicited a magnitude of response of 88 SFC with a functional avidity of 1nM.

**HXB2 Location** RT (392–401)

**Author Location**

**Epitope** PIQKETWETW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A32)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (A32), an additional HLA (A24) was statistically predicted to be associated with this epitope.

**HXB2 Location** RT (397–406)

**Author Location** RT (LAI)

**Epitope** TWETWWTEYW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**References** Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Recognized by CTL from two progressors, EILKEPVGHGV and EELRQHLLRW were also recognized by one, and RETKLGKAGY was also recognized by the other.

**HXB2 Location** RT (397–406)

**Author Location** RT Pol (552–561)

**Epitope** TWETWWTEYW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 11 patients recognized this epitope.

**HXB2 Location** RT (407–416)

**Author Location** (C consensus)

**Epitope** QATWIPEWEF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5702)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- QATWIPEWEF is an optimal epitope for both B\*5702 and B\*5703.

**HXB2 Location** RT (407–416)

**Author Location** (C consensus)

**Epitope** QATWIPEWEF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5703)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- QATWIPEWEF is an optimal epitope for both B\*5702 and B\*5703.

**HXB2 Location** RT (407–416)

**Author Location** (C consensus)

**Epitope** QATWIPEWEF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** RT (413–429)

**Author Location** (C consensus)

**Epitope** EWEFVNRPLVQLWYQL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (416–423)

**Author Location** Pol (571–)

**Epitope** FVNTPLLVK

**Epitope name** Pol571

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* RT  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** transgenic mouse (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced a CTL responses 1/6 transgenic mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

**HXB2 Location** RT (416–424)

**Author Location** RT (416–424)

**Epitope** FVNTPLLVK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, SPRTLNAWV, was predicted to be restricted by HLA A\*1101.

**HXB2 Location** RT (416–424)

**Author Location** Pol (563–571 93TH253 subtype CRF01)

**Epitope** FVNTPLLVK

**Epitope name** P571-579

**Subtype** CRF01\_AE

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 128 who was HLA A11/A33.

**HXB2 Location** RT (416–424)

**Author Location** Pol (563–571 93TH253 subtype CRF01)

**Epitope** FVNTPLLVK

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 1/8 tested FSWs recognized it.
- This epitope was conserved many subtypes (but not subtype H), but exact matches were not very common.

**HXB2 Location** RT (419–429)

**Author Location** RT (419–429)

**Epitope** TPPLVKLWYQL

**Epitope name** TL11

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other

**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism

**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction

**HXB2 Location** RT (421–429)

**Author Location** Pol

**Epitope** PLVKLWYQL

**Epitope name** P9L

**Immunogen** vaccine

*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3

**Species (MHC)** transgenic mouse (A\*0201)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells

**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** RT (421–429)

**Author Location** RT (421–429)

**Epitope** PLVKLWYQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.

- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.

- This epitope, PLVKLWYQL, was predicted to be restricted by HLA A\*0201, A\*0202 and A\*0203.

**HXB2 Location** RT (421–429)

**Author Location** RT (421–429)

**Epitope** PLVKLWYQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Haas *et al.* 1998

- Of 98 patients in cross-sectional analysis, 78% had CTL against pol - RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
- New clusters of epitopes were defined utilizing different HLA molecules.

**HXB2 Location** RT (428–445)

**Author Location** RT

**Epitope** QLEKEPIVGAETFYVDGA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J.Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.

- This immunodominant, frequently targeted overlapping peptide, QLEKEPIVGAETFYVDGA, had an overall frequency of recognition of 15.3% - 22% AA, 11.5% C, 4.5% H, 23.8% WI.

**HXB2 Location** RT (432–440)

**Author Location** RT (587–597 SF2)

**Epitope** EPIVGAETF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**Keywords** review

**References** Menendez-Arias *et al.* 1998; Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- 5/7 B35-positive individuals had a CTL response to this epitope.
- An E to D substitution at position 1, and V to I at position 4, reduces activity but not binding to B\*3501.
- Menendez-Arias *et al.* [1998] note in their review that this epitope is near the protease cleavage site and conservation of this region is important for proper viral maturation.

**HXB2 Location** RT (432–440)

**Author Location** Pol (587–595)

**Epitope** EPIVGAETF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**References** Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B\*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

**HXB2 Location** RT (432–440)

**Author Location**

**Epitope** EPIVGAETF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** acute/early infection

**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWILGGLNK.

- The subject with A\*0201 had a moderately strong response to SLYNTVATL.

- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.

- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** RT (432–440)

**Author Location** Pol (587–595)

**Epitope** EPIVGAETF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Dyer *et al.* 1999

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

**HXB2 Location** RT (432–440)

**Author Location** Pol

**Epitope** EPIVGAETF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- No one, 0/3 HLA B35+ infection-resistant men, and 0/5 pre-seroconversion men who went on to become infected, reacted to this epitope.

**HXB2 Location** RT (432–440)

**Author Location** RT (587–596 SF2)

**Epitope** EPIVGAETF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35, B51)

**References** Shiga *et al.* 1996

- Binds HLA-B\*3501, and is also presented by B51 – but CTL could not kill RT-vaccinia virus infected cells that expressed B51.

**HXB2 Location** RT (432–440)

**Author Location** Pol (587–595)

**Epitope** EPIVGAETF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35, B51)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** RT (432–440)

**Author Location** RT (432–440)

**Epitope** EPIVGAETF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** RT (432–441)

**Author Location** Pol (587–596)

**Epitope** EPIVGAETFY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**References** Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B\*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

**HXB2 Location** RT (432–441)

**Author Location** RT (587–597 SF2)

**Epitope** EPIVGAETFY

**Immunogen** HIV-1 infection

**Species (MHC)** mouse (B35)

**Keywords** review

**References** Menendez-Arias *et al.* 1998; Shiga *et al.* 1996

- Binds HLA-B\*3501, but not presented by B51, in contrast to the peptide EPIVGAETF.
- Menendez-Arias *et al.* [1998] note in their review that this epitope is located near the protease cleavage site and conservation of this region is important for viral maturation.

- This epitope spans the Pol p66 RT – p15 (RNase) domain.

**HXB2 Location** RT (432–441)

**Author Location** RT (587–597 SF2)

**Epitope** EPIVGAETFY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** rate of progression

**References** Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation.

**HXB2 Location** RT (432–441)

**Author Location** Pol (587–596)

**Epitope** EPIVGAETFY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35, B51)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30–40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- None of seven patients responded to this peptide with GzB producing cells, while two of the patients responded with IFN-gamma producing cells.

**HXB2 Location** RT (434–447)

**Author Location** RT (LAI)

**Epitope** IVGAETFYVDGAAS

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6802)

**References** Menendez-Arias *et al.* 1998; van der Burg *et al.* 1997

- Recognized by CTL from a long-term survivor that recognized a set of 5 overlapping peptides spanning IVGAETFYVDGAAS as well as PIVLPEKDSW and KITTESIVIW.
- A\*6802 is a subset of HLA-A28.
- This epitope spans the Pol p66 RT – p15 (RNase) domain.

**HXB2 Location** RT (436–445)

**Author Location** (C consensus)

**Epitope** GAETFYVDGA

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6802)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$



**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- GAETFYVDGA is an optimal epitope.

**HXB2 Location** RT (436–445)

**Author Location** RT (436–445)

**Epitope** GAETFYVDGA

**Immunogen**

**Species (MHC)** human (A\*6802)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an A\*6802 epitope.

**HXB2 Location** RT (436–445)

**Author Location** RT (591–600 IIIB)

**Epitope** GAETFYVDGA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B45)

**References** Menendez-Arias *et al.* 1998

- This epitope spans the Pol p66 RT – p15 (RNase) domain.

**HXB2 Location** RT (436–445)

**Author Location** Pol (591–600 IIIB)

**Epitope** GVETFYVDGA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B45)

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- No variants of this epitope were found in a non-transmitting mother who had a CTL response to it.
- This epitope spans the Pol p66 RT – p15 (RNase) domain.

**HXB2 Location** RT (436–452)

**Author Location** (C consensus)

**Epitope** GAETFYVDGAANRETKI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3402)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (436–452)

**Author Location** (C consensus)

**Epitope** GAETFYVDGAANRETKI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (436–452)

**Author Location** RT

**Epitope** GAETFYVDGAANRETKL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, GAETFYVDGAANRETKL, had an overall frequency of recognition of 18% - 20.3% AA, 11.5% C, 18.2% H, 19% WI.

**HXB2 Location** RT (437–445)

**Author Location**

**Epitope** AETFYVDGA

**Epitope name** Pol-AA9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4501)  
**Donor MHC** A\*3002, A\*3201, B\*4501, B\*5301, Cw\*0401, Cw\*1202  
**Keywords** HAART, ART  
**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 00RCH33 was on HAART had a viral load of 2900 and CD4 count of 727 and also recognized the epitopes YPLT-FGWY, Nef(135-143), HLA B\*5301; RSLYNTVATLY, p17(76-86), HLA A\*3002; and HIGPGRAFY, gp160(310-318), HLA A\*3002.
- Among HIV+ individuals who carried HLA B45, 3/9 (33%) recognized this epitope.

**HXB2 Location** RT (437–447)  
**Author Location** RT (592–602 LAI)  
**Epitope** AETFYVDGAAN  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (A28)  
**References** Brander & Walker 1996; Menendez-Arias *et al.* 1998

- P. Johnson, pers. comm.
- This epitope spans the Pol p66 RT – p15 (RNase) domain.

**HXB2 Location** RT (437–447)  
**Author Location** Pol (592–602)  
**Epitope** AETFYVDGAAN  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A28)  
**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** RT (438–448)  
**Author Location** (C consensus)  
**Epitope** ETFYVDGAANR  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*66)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- ETFYVDGAANR is an optimal epitope.

**HXB2 Location** RT (438–448)  
**Author Location** RT (593–603 IIIB)  
**Epitope** ETFYVDGAANR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A26)  
**References** Menendez-Arias *et al.* 1998

- This epitope spans the Pol p66 RT – p15 (RNase) domain.

**HXB2 Location** RT (438–448)  
**Author Location** Pol (593–603 IIIB)  
**Epitope** ETFYVDGAANR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A26)  
**Keywords** responses in children, mother-to-infant transmission, escape  
**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- One other variant was found that gave a positive, though reduced, CTL response: ETYYVNGAANR.
- This epitope spans the Pol p66 RT – p15 (RNase) domain.

**HXB2 Location** RT (438–448)  
**Author Location** RT  
**Epitope** ETFYVDGAANR  
**Epitope name** A26-ER11(RT)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A26)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (438–448)  
**Author Location**  
**Epitope** ETFYVDGAANR  
**Epitope name** ER11  
**Immunogen**  
**Species (MHC)** human (A66)  
**Keywords** optimal epitope

- References** Frahm *et al.* 2008
- C. Brander notes this is a A66 epitope.

**HXB2 Location** RT (440–448)  
**Author Location** Pol (594–602 SF2)  
**Epitope** FYVDGAANR  
**Subtype** B  
**Immunogen** HIV-1 infection, computer prediction  
**Species (MHC)** human (A\*3303)  
**Assay type** Chromium-release assay  
**Keywords** binding affinity, computational epitope prediction

- References** Hossain *et al.* 2003
- HLA-A\*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A\*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A\*3303. Six of these served as peptide-targets for lysis by PBMC from infected individual, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
  - This epitope is one of the 4 that are properly processed.

**HXB2 Location** RT (448–457)  
**Author Location** RT  
**Epitope** RETKLGKAGY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A29)  
**Keywords** rate of progression  
**References** van der Burg *et al.* 1997

- Patients studied were from the Amsterdam cohort.
- CTL epitopes of 3 rapid progressors were compared to 4 long-term survivors (LTS) and no differences could be found in the degree of conservation between them.
- Epitope recognized by a LTS.
- This epitope occurs in the p15 (RNase) domain of Pol p66 RT.

**HXB2 Location** RT (449–457)  
**Author Location**  
**Epitope** ETKLGKAGY  
**Epitope name** Pol-EY9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2601)  
**Donor MHC** A\*2601, A\*3303, B\*5801, B\*8201, Cw\*0302, Cw\*0701  
**Keywords** HAART, ART  
**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 03RCH40 was African American, had a viral load of 2500, CD4 count of 372, was not on HAART, and also recognized the epitope DILDWLWY, Nef(108-115), HLA Cw\*0701.

- Among HIV+ individuals who carried HLA A26, 2/8 (25%) recognized this epitope.

**HXB2 Location** RT (449–457)  
**Author Location** Pol (604–612)  
**Epitope** ETKLGKAGY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2601)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** RT (449–457)  
**Author Location** Pol (604–612)  
**Epitope** ETKLGKAGY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2601)  
**Country** Japan  
**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay, Other, HLA binding  
**Keywords** immunodominance, characterizing CD8+ T cells, optimal epitope  
**References** Satoh *et al.* 2005

- Reverse immunogenetics was used to identify HIV-1 epitopes presented by HLA-A\*2601. Four epitopes endogenously presented by this allele induced peptide-specific CD8 T-cells. HIV-infected individuals predominantly detected 2 of the epitopes, which might be useful for vaccine development. HLA-A\*2601 is common in Asia.
- Immunodominant epitope recognized in 4/6 HIV-infected individuals with HLA-A\*2601. This epitope is highly conserved in clade E (CRF01), and moderately conserved in clade B.

**HXB2 Location** RT (449–457)  
**Author Location** Pol  
**Epitope** ETKLGKAGY  
**Epitope name** A26-EY9(pol)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A26)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** RT (451–459)

**Author Location** Pol (606–)

**Epitope** KLGKAGYVT

**Epitope name** Pol606

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* RT  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder that did not induce CTL or CD8+ T-cell IFN gamma responses in transgenic mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

**HXB2 Location** RT (467–484)

**Author Location** (C consensus)

**Epitope** VSLTETTNQKTELQAIQL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*18)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** RT (481–505)

**Author Location** RT (648–672 PV22)

**Epitope** AIYLALQDSGLEVNIVTDSQYALGI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Kalams *et al.* 1994; Menendez-Arias *et al.* 1998

- A CTL response used to study gene usage in HLA-B14 response.
- This epitope occurs in the p15 (RNase) domain of Pol p66 RT.

**HXB2 Location** RT (481–505)

**Author Location** RT (648–672)

**Epitope** AIYLALQDSGLEVNIVTDSQYALGI

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Menendez-Arias *et al.* 1998; Price *et al.* 1995

- Study of cytokines released by HIV-1 specific activated CTL.

- This epitope occurs in the p15 (RNase) domain of Pol p66 RT.

**HXB2 Location** RT (485–493)

**Author Location** RT (485–493)

**Epitope** ALQDSGLEV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, ALQDSGLEV, was detected within overlapping peptides QKTELQAIHLALQDSGL and IHLALQDSGLEVNIV.

**HXB2 Location** RT (485–493)

**Author Location** RT (640–648 HXB2R)

**Epitope** ALQDSGLEV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Brander *et al.* 1995; Brander *et al.* 1996

- This epitope was recognized by PBMC from 3/14 HIV+ asymptomatic patients.
- This epitope was used along with Env CTL epitope TLTSC-NTSV and a tetanus toxin T helper epitope for a synthetic vaccine.
- This vaccine failed to induce a CTL response, although a helper response was evident.
- This epitope occurs in the p15 (RNase) domain of Pol p66 RT.

**HXB2 Location** RT (485–493)

**Author Location** RT (640–648 HXB2R)

**Epitope** ALQDSGLEV

**Immunogen** vaccine

*Strain:* B clade HXB2 *HIV component:* RT

**Species (MHC)** human (A2)

**References** Brander *et al.* 1995

- Epitope studied in the context of inclusion in a synthetic vaccine.
- This epitope occurs in the p15 (RNase) domain of Pol p66 RT.

**HXB2 Location** RT (485–493)

**Author Location** Pol (649–659 BH10, LAI)

- Epitope** ALQDSGLEV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Maksiutov *et al.* 2002
- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
  - This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is IYLAALQDSGLE) has similarity with the epidermal growth factor receptor kinase substrate EPS8, fragment ISAAASDSGVE.
- HXB2 Location** RT (485–494)  
**Author Location** RT (485–495 HXB2)  
**Epitope** ALQDSGSEVN  
**Epitope name** 51H  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* multiple epitope immunogen *HIV component:* p17/p24 *Gag, Pol Adjuvant:* IL-12  
**Species (MHC)** transgenic mouse (A2)  
**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** vaccine-specific epitope characteristics, vaccine antigen design  
**References** Bolesta *et al.* 2005
- Immunization of transgenic mice with a codon-optimized hGagp17p24-Polp51 DNA plasmid, consisting of clusters of highly conserved CTL epitopes presented by multiple MHC class I alleles, induced 2- to 5-fold higher CD8+ T-cell responses than the corresponding full-length proteins. The modified proteins had the ribosomal frameshift deleted, as well as the potentially immunosuppressive p15, and protease and integrase. This correlated with higher protection against challenge with Gag and Pol expressing recombinant vaccinia virus. Mice immunized with the hGagp17p24-Polp51 also showed an elevated level of type 1 cytokine production as well as an increased titer of p24- and RT-specific IgG2 antibody responses.
  - This was 1 of 4 A2 gag/pol epitopes tested. Transgenic mice immunized with the deleted construct induced more potent EliSpot reactions to this epitope than those immunized with full length Gag/Pol.
- HXB2 Location** RT (485–505)  
**Author Location** RT (648–672)  
**Epitope** ALQDSGLEVVTDTSQYALGI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**References** Brander & Walker 1995
- Unpublished, S. Kalams.
  - This epitope occurs in the p15 (RNase) domain of Pol p66 RT.
- HXB2 Location** RT (492–501)  
**Author Location** Pol (647–656)  
**Epitope** EVNIVTDSQY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2601)

- Country** Japan  
**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay, Other, HLA binding  
**Keywords** immunodominance, optimal epitope  
**References** Satoh *et al.* 2005
- Reverse immunogenetics was used to identify HIV-1 epitopes presented by HLA-A\*2601. 110 peptides were predicted to bind to HLA-A\*2601. 24 of these were demonstrated to bind through a HLA-A\*2601 stabilization assay. Four of these, including this one, were shown to be epitopes endogenously presented by this allele, that can induce peptide-specific CD8 T-cells. HLA-A\*2601 is common in Asia.
  - This epitope was recognized in only 1/7 HLA-A\*2601 HIV infected individuals.
- HXB2 Location** RT (492–506)  
**Author Location** (C consensus)  
**Epitope** EVNIVTDSQYALGII  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3910)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HXB2 Location** RT (492–506)  
**Author Location** (C consensus)  
**Epitope** EVNIVTDSQYALGII  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*0802)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HXB2 Location** RT (493–502)  
**Author Location** Pol (648–657)  
**Epitope** VNIIVTDSQYA  
**Subtype** B  
**Immunogen** HIV-1 infection, peptide-HLA interaction  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** immunodominance  
**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, VNIVTDSQYA, is similar to human protein HERV, sequence VNIyTDSQYA and human protein Thrombospondin 3 precursor, sequence VNtVTDDdYA.

**HXB2 Location** RT (495–503)

**Author Location**

**Epitope** IVTDSQYAL

**Epitope name** IL9

**Immunogen**

**Species (MHC)** human (Cw\*0802)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a Cw\*0802 epitope.

**HXB2 Location** RT (496–505)

**Author Location**

**Epitope** VTDSQYALGI

**Epitope name** Pol-VII10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Donor MHC** A\*3002, A\*6801, B\*0801, B\*1503, Cw\*0701, Cw\*08

**Keywords** HAART, ART

**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 01RCH51 was an African American on HAART, viral load 980, CD4 count 811.
- Among HIV+ individuals who carried HLA B15, 1/17 (6%) recognized this epitope.

**HXB2 Location** RT (496–505)

**Author Location** Pol (651–660)

**Epitope** VTDSQYALGI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** RT (496–505)

**Author Location** Pol (651–660)

**Epitope** VTDSQYALGI

**Epitope name** VII10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Donor MHC** A\*02, A\*68, B\*14, B\*52, Cw\*08, Cw\*12

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** escape, optimal epitope

**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The B consensus form of this epitope, VTDSQYALGI, persisted throughout 6 years of chronic infection in 1 individual.

**HXB2 Location** RT (496–505)

**Author Location** Pol (subtype B)

**Epitope** VTDSQYALGI

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B\*1402, B14)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B and D clade viruses.

**HXB2 Location** RT (496–505)

**Author Location** RT (663–672 IIIB)

**Epitope** VTDSQYALGI

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**References** Brander & Walker 1996

- Unpublished, P. Johnson.
- Published in this database in 1995 as B14, but B14 transfected cells did not present the peptide and it is thought to be presented by the genetically linked Cw8 molecule instead Brander & Walker [1996]
- This epitope occurs in the p15 (RNase) domain of Pol p66 RT.

**HXB2 Location** RT (496–505)

**Author Location** RT

**Epitope** VTDSQYALGI

- Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (Cw8)  
**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)  
**References** Rowland-Jones *et al.* 1998a
- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
  - The A and D subtype consensus are identical to the B clade epitope.
  - Thought to be HLA-Cw8 restricted, not B14 as originally reported (C. Brander, B. Walker, and S. Rowland-Jones, personal communication)
  - This epitope occurs in the p15 (RNase) domain of Pol p66 RT.
- HXB2 Location** RT (497–512)  
**Author Location** (C consensus)  
**Epitope** TDSQYALGIIQAQPKD  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0205)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HXB2 Location** RT (502–517)  
**Author Location** (C consensus)  
**Epitope** ALGIIQAQPKSESEL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3901)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HXB2 Location** RT (509–518)  
**Author Location** Pol  
**Epitope** QPDKSESELV  
**Immunogen**  
**Species (MHC)** human (B7)  
**References** De Groot *et al.* 2001
- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFN $\gamma$  production in an ELISPOT assay.
  - QPDKSESELV was newly identified as an HLA-B7 epitope in this study.
- HXB2 Location** RT (509–518)  
**Author Location** Pol  
**Epitope** QPDKSESELV  
**Epitope name** 1302  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Donor MHC** A03, A24, B07, B38, Cw07, Cw12/13  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, computational epitope prediction  
**References** De Groot *et al.* 2003
- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
  - Estimated binding probability for QPDKSESELV: 36%
- HXB2 Location** RT (516–525)  
**Author Location** RT (516–525)  
**Epitope** ELVNQIIEQL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Haas *et al.* 1998
- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
  - New clusters of epitopes were defined utilizing different HLA molecules.
  - This epitope occurs in the p15 (RNase) domain of Pol p66 RT.
- HXB2 Location** RT (520–528)  
**Author Location** Pol (520–528 LAI)  
**Epitope** QIIEQLIKK  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (A\*1101)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008; Fukada *et al.* 1999
- C. Brander notes this is an A\*1101 epitope.
- HXB2 Location** RT (520–528)  
**Author Location** Pol (675–683)  
**Epitope** QIIEQLIKK  
**Subtype** B, CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*1101)  
**Keywords** subtype comparisons, TCR usage

**References** Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A\*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A\*1101 epitopes was recognized in a clade specific manner. Two other HLA A\*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- QIIEQLIKK was found to elicit clade-specific responses in clade B (QIIEQLIKK is most common) and clade E (qiieElikk is most common). QIIEQLIKK was strongly recognized by CTL from 1/5 B clade infected Japanese subjects, and qiieElikk from 3/7 E clade infected Thai subjects. The variant qiieKliEk, common in the A subtype, was also recognized in 2/7 E clade infected Thai subjects.
- The binding of QIIEQLIKK, qiieElikk and qiieKliEk to HLA A\*1101 was similar, but CTL clones from individuals did not cross-react with the cross-clade peptides indicating that the substitutions inhibited TCR interaction.

**HXB2 Location** RT (520–528)**Author Location** RT (80–88)**Epitope** QIIEQLIKK**Immunogen** HIV-1 infection**Species (MHC)** human (A\*1101)**Keywords** optimal epitope**References** Frahm *et al.* 2008**HXB2 Location** RT (520–528)**Author Location** Pol (676–684)**Epitope** QIIEQLIKK**Epitope name** QK9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A11)**Donor MHC** A11, A2, B18, B44, Cw12, Cw5**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay**Keywords** optimal epitope**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

**HXB2 Location** RT (520–528)**Author Location** Pol (676–684)**Epitope** QIIEQLIKK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A11)**Donor MHC** A11, A2, B18, B44, Cw12, Cw5**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** RT (520–528)**Author Location** Pol**Epitope** QIIEQLIKK**Epitope name** 1336**Subtype** multiple**Immunogen** HIV-1 infection**Species (MHC)** human (A3)**Donor MHC** A03, A23, B49, B57**Assay type** T-cell Elispot**Keywords** binding affinity, computational epitope prediction**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for QIIEQLIKK: 48%

**HXB2 Location** RT (530–538)**Author Location****Epitope** KVYLAWVPA**Epitope name** Pol-KA9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Donor MHC** A\*0202, A\*0301, B\*4501, B\*5301, Cw\*0401, Cw\*1502**Keywords** HAART, ART**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 04RCH86 was Hispanic, not on HAART, and had a viral load of 7600 and CD4 count of 1774.
- Among HIV+ individuals who carried HLA A\*03, 2/21 (10%) recognized this epitope.

**HXB2 Location** RT (530–538)**Author Location** Pol (685–693)**Epitope** KVYLAWVPA



- Epitope name** KA9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay  
**Keywords** escape, acute/early infection  
**References** Bansal *et al.* 2005
- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
  - The response to this epitope was barely detectable until month 41.
- HXB2 Location** RT (530–538)  
**Author Location** Pol (680–691 BH10, LAI)  
**Epitope** KVVYLAWVPA  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Maksutov *et al.* 2002
- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
  - This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is IKKEKVY-LAWV) has similarity with B-cell growth factor precursor, fragment IKKERLWLGPV.
- HXB2 Location** RT (530–540)  
**Author Location** (C consensus)  
**Epitope** RVYLSWVPAHK  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** epitope processing, rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - Mutational patterns in a residue outside of the optimized epitope of RVYLSWVPAHK are associated with the presence of the HLA presenting molecule in the host.
- HXB2 Location** RT (532–540)  
**Author Location** Pol (687–)  
**Epitope** YLAWVPAHK  
**Epitope name** Pol687  
**Immunogen** HIV-1 infection, vaccine

**Vector/Type:** peptide **HIV component:** RT  
**Adjuvant:** Incomplete Freund's Adjuvant (IFA)

- Species (MHC)** human, transgenic mouse (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction  
**References** Corbet *et al.* 2003
- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
  - This peptide was an intermediate A2 binder, and induced a CD8+ T-cell IFN gamma response in 1/6 mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.
- HXB2 Location** RT (532–540)  
**Author Location** Pol (714–722)  
**Epitope** YLAWVPAHK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3 supertype)  
**Keywords** supertype, rate of progression  
**References** Propato *et al.* 2001
- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
  - Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
  - A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
  - This epitope can bind 5/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).
- HXB2 Location** RT (532–540)  
**Author Location** RT (532–540)  
**Epitope** YLAWVPAHK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**References** Haas *et al.* 1998
- Of 98 patients in cross-sectional analysis, 78% had CTL against pol – RT was more immunogenic than Integrase and Protease (81%, 51%, and 24% of 37 patients, respectively)
  - New clusters of epitopes were defined utilizing different HLA molecules.
  - This epitope occurs in the p15 (RNase) domain of Pol p66 RT.
- HXB2 Location** RT (532–540)  
**Author Location** RT Pol (687–695)  
**Epitope** YLAWVPAHK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/7 patients recognized this epitope.

## II-B-13 RT-Integrase CTL/CD8+ epitopes

**HXB2 Location** RT-Integrase (553–2)

**Author Location** Pol

**Epitope** STGIRRVLFL

**Epitope name** SL10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A28, A29, B14, B44, Cw8

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- An escape mutation at position 6 (stgirKvlf) was found not to correspond to the most polymorphic residues in the epitope. This is a novel partially mapped epitope.

**HXB2 Location** RT-Integrase (560–8)

**Author Location** Pol (715–723)

**Epitope** LFLDGIDKA

**Immunogen**

**Species (MHC)** human (B81)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

## II-B-14 Integrase CTL/CD8+ epitopes

**HXB2 Location** Integrase (9–19)

**Author Location** (C consensus)

**Epitope** QEEHEKYHSNW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4403)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the E2 and E3 residues of QEEHEKYHSNW are associated with the presence of the HLA presenting molecule in the host.
- QEEHEKYHSNW not optimized.

**HXB2 Location** Integrase (9–19)

**Author Location** Pol

**Epitope** QEEHEKYHSNW

**Epitope name** QW11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A28, A29, B14, B44, Cw8

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 2, qAehekyhsnw, was found not to correspond to the most polymorphic residues in the epitope. This is a novel partially mapped epitope.

**HXB2 Location** Integrase (20–28)

**Author Location** Integrase (20–28)

**Epitope** RAMASDFNL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.

- This epitope, RAMASDFNL, was predicted to be restricted by HLA A\*0201, B\*2709 and C\*0304

**HXB2 Location** Integrase (20–28)  
**Author Location** Pol (762–770)  
**Epitope** RAMASDFNL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2 supertype)  
**Keywords** supertype, rate of progression  
**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

**HXB2 Location** Integrase (22–31)  
**Author Location** Pol (764–773)  
**Epitope** MASDFNLPPV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2 supertype)  
**Keywords** supertype, rate of progression  
**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802)

**HXB2 Location** Integrase (28–36)  
**Author Location** (C consensus)  
**Epitope** LPPIVAKEI  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0705)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- LPPIVAKEI is an optimal epitope for B\*4201, B\*0705, and B\*5101.

**HXB2 Location** Integrase (28–36)  
**Author Location** (C consensus)  
**Epitope** LPPIVAKEI  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Integrase (28–36)  
**Author Location** (C consensus)  
**Epitope** LPPIVAKEI  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the P3, I4, A6, and K7 residues of LPPIVAKEI are associated with the presence of the HLA presenting molecule in the host.
- LPPIVAKEI is an optimal epitope for B\*4201, B\*0705, and B\*5101.

**HXB2 Location** Integrase (28–36)  
**Author Location** Integrase (27–36)  
**Epitope** LPPIVAKEI  
**Epitope name** LI9  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other  
**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism

**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- A strong association between B\*4201 and variation in this epitope was found.

**HXB2 Location** Integrase (28–36)**Author Location** Integrase (28–36)**Epitope** LPPIVAKEI**Epitope name** LI9**Immunogen** peptide-HLA interaction**Species (MHC)** human (B\*4201)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding**Keywords** optimal epitope**References** Honeyborne *et al.* 2006

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B\*3910, B\*4201, B\*8101 and Cw\*1801, by motif inference. HLA-A\*2902 was found to overlap those of A1 and A24 superotypes.
- LPPIVAKEI (LI9) was the optimal epitope for HLA-B\*4201 with variants LPPIVAKE, PPIVAKEI, LPPIVAKEIv, nLPPIVAKEI having been tested.

**HXB2 Location** Integrase (28–36)**Author Location** Integrase**Epitope** LPPIVAKEI**Epitope name** LI9**Immunogen** HIV-1 infection**Species (MHC)** human (B\*51)**Country** Australia**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape, HLA associated polymorphism**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore *et al.*, *Science* 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- There are two variant forms of this B57/B5801 epitope at the second position, LPPIVAKEI and LPPVVAKEI. Leslie *et al.*, *J Exp Med.* 201:891 (2005) suggest that the escape form LPPVVAKEI may have come to dominate the B clade lineage over

time due to higher HLA B51 frequencies in B clade epidemic regions. Bhattacharya suggests lineage effects are also playing an important role in the observed amino acid frequencies, and note that the ratio of I/V has not change over time, and that the frequency of I/V in different epidemic populations does not correlate with HLA B51 allele frequency.

**HXB2 Location** Integrase (28–36)**Author Location** Pol (743–751 SF2)**Epitope** LPPVVAKEI**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5101)**Keywords** subtype comparisons, rate of progression**References** Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (*Nat. Med.* 2:405, 1996; *Lancet* 22:1187, 1986; *Hum Immunol* 22:73, 1988; *Hum Immunol* 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B\*5101 anchor residues, 33 bound to HLA-B\*5101, seven of these peptides were reactive with CTL from 3 B\*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences – LPPVVAKEI is highly conserved.

**HXB2 Location** Integrase (28–36)**Author Location** (C consensus)**Epitope** LPPIVAKEI**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5101)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- LPPIVAKEI is an optimal epitope for B\*4201, B\*0705, and B\*5101.

**HXB2 Location** Integrase (28–36)**Author Location** Integrase (28–36 HXB2)**Epitope** LPPVVAKEI**Epitope name** LI9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5101)**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape, immune evasion, optimal epitope**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

**HXB2 Location** Integrase (28–36)

**Author Location** Pol (743–749 NL-432)

**Epitope** LPPVVAKEI

**Immunogen** HIV-1 infection

**Species (MHC)** (B\*5101)

**Assay type** Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay, CTL suppression of replication

**Keywords** binding affinity, class I down-regulation by Nef, rate of progression

**References** Tomiyama *et al.* 2005

- HLA-B\*5101 associated with slow progression to the disease state was studied as related to Nef-mediated HLA class I downregulation. It was shown that different CTLs have different ranges of ability to kill HIV-1 infected CD4+ T cells and suppress HIV-1 replication. This was found to be a function of the specific HIV-1 epitope presented by the corresponding HLA allele to the CTL.
- Certain epitope-recognising CTL clones or lines were therefore capable of killing HIV-1 infected cells even in the presence of Nef-mediated MHC 1 downregulation, while other CTL clones recognising different epitopes were not so capable.
- There was no significant difference in cytokine production or cytokine producing cells between CTLs that were capable of killing CD4+ T-cells infected with HIV-1 and those CTLs that could not kill such HIV-1 infected cells.
- On the basis of studies involving binding abilities and cytolytic activities for four different epitopes that correlate with HLA-B\*5101-restricted CTLs, it is suggested that the ability of CTLs to kill infected CD4+ T cells is due to the number of epitopes presented by the HLA on the surface of the CD4+ T cells rather than the ability of TCR to recognise the epitope.

**HXB2 Location** Integrase (28–36)

**Author Location**

**Epitope** LPPIVAKEI

**Epitope name** LI9

**Immunogen**

**Species (MHC)** human (B42)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B42 epitope.

**HXB2 Location** Integrase (28–36)

**Author Location** Pol (28–36)

**Epitope** LPPVVAKEI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. The lpplvakei variant arose at intermediate time points.

**HXB2 Location** Integrase (28–36)

**Author Location** Integrase (28–36)

**Epitope** LPPIVAKEI

**Epitope name** LI9

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding

**Keywords** subtype comparisons, computational epitope prediction, mother-to-infant transmission, escape, viral fitness and reversion, optimal epitope

**References** Leslie *et al.* 2005

- An I4V substitution (LPPvVAKEI) is suggested to be driven by CTL escape in B51-positive subjects. The escape form is the consensus form of the epitope in the B clade, and stable in the absence of HLA-B51. In the C clade the B51 is rare, and the Val escape mutation is also rare.

**HXB2 Location** Integrase (28–36)

**Author Location** Integrase

**Epitope** LPPVVAKEI

**Epitope name** B51-LI9(Int)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Integrase (29–46)

**Author Location** (C consensus)

**Epitope** PPIVAKEIVASCDKQCLK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Integrase (37–45)

**Author Location** Integrase (37–45)

**Epitope** VASCDKQCL

**Epitope name** VL9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other

**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism

**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction

**HXB2 Location** Integrase (53–60)

**Author Location** Integrase (54–61)

**Epitope** QVDCSPGI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, QVDCSPGI, of unknown HLA restriction, was detected within overlapping peptides LKGEAMHGQVDCSPGIW and GQVDCSPGIWQLDCTHL.

**HXB2 Location** Integrase (62–71)

**Author Location** Pol

**Epitope** QLDCTHLEGGK

**Epitope name** 1335

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, A23, B49, B57; A03, A11, B05, B14, Cw08

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC superotypes.
- Estimated binding probability for QLDCTHLEGGK: 61%.

**HXB2 Location** Integrase (66–74)

**Author Location** (C consensus)

**Epitope** THLEGGKIIL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1510)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the L9 residue of THLEGGKIIL are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** Integrase (66–74)

**Author Location**

**Epitope** THLEGGKIIL

- Epitope name** TIL9  
**Immunogen**  
**Species (MHC)** human (B\*1510)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is a B\*1510 epitope.
- HXB2 Location** Integrase (82–89)  
**Author Location** RT (797–804 SF2)  
**Epitope** GYIEAEVI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2402)  
**References** Ikeda-Moore *et al.* 1997
- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
  - This peptide induced CTL in 1/4 HIV-1 + people tested.
  - GYIEAEVI bound to A\*2402 weakly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.
- HXB2 Location** Integrase (83–91)  
**Author Location** Pol (798–806)  
**Epitope** YIEAEVIPA  
**Subtype** B  
**Immunogen** HIV-1 infection, peptide-HLA interaction  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** immunodominance  
**References** Rolland *et al.* 2007b
- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
  - Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
  - This HIV-1 epitope, YIEAEVIPA, is similar to an unnamed human protein, sequence gYIEAaVIPAG and human protein p53 inducible protein, sequence EIEAEV.
- HXB2 Location** Integrase (89–98)  
**Author Location** Pol  
**Epitope** IPAETGQETA  
**Immunogen**  
**Species (MHC)** human (B56)  
**References** De Groot *et al.* 2001
- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.

- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFN $\gamma$  production in an ELISPOT assay.
- IPAETGQETA was newly identified as an HLA-B56 epitope in this study.

- HXB2 Location** Integrase (89–98)  
**Author Location** Pol  
**Epitope** IPAETGQETA  
**Epitope name** 1294  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Donor MHC** A02, A03, B07, B58, Cw07  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, computational epitope prediction  
**References** De Groot *et al.* 2003
- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
  - Estimated binding probability for IPAETGQETA: 8%

- HXB2 Location** Integrase (89–98)  
**Author Location** Pol (805–814 BH10, LAI)  
**Epitope** IPAETGQETA  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Maksutov *et al.* 2002
- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
  - This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is PAETGQETAY) has similarity with Integrin beta-4 precursor (GP150)(CD104), fragment PAETNGEITAY.

- HXB2 Location** Integrase (90–107)  
**Author Location** (C consensus)  
**Epitope** PAETGQETAYFILKLAGR  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*6802)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- HXB2 Location** Integrase (92–99)  
**Author Location** (C consensus)

**Epitope** ETGQETAY**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2601)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- ETGQETAY is an optimal epitope.

**HXB2 Location** Integrase (96–104)**Author Location** Integrase (823–831)**Epitope** ETAYFILKL**Immunogen****Species (MHC)** human (A\*6802)**Keywords** subtype comparisons**References** Dong & Rowland-Jones 1998

- Epitope found in clade A, B, and D – pers. comm. S. Rowland-Jones and T. Dong.

**HXB2 Location** Integrase (96–104)**Author Location** Pol (subtype A)**Epitope** ETAYFILKL**Subtype** A**Immunogen** HIV-1 exposed seronegative**Species (MHC)** human (A\*6802)**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNT-VATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** Integrase (96–104)**Author Location** Pol**Epitope** ETAYFILKL**Immunogen** HIV-1 infection**Species (MHC)** human (A\*6802)**Keywords** HIV exposed persistently seronegative (HEPS)**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.

- This epitope was recognized in 1/22 HEPS sex worker controls (ML1671)

**HXB2 Location** Integrase (96–104)**Author Location** Pol (744–752)**Epitope** ETAYFILKL**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human (A\*6802)**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance**References** Kaul *et al.* 2001a

- ETAYFILKL cross-reacts with clades A, B and D.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A\*6802 women, 3/12 HEPS and 9/11 HIV-1 infected women recognized this epitope likelihood ratio 7.9, p value 0.01, and HEPS women tended to respond to DTVLEDINL, while infected women to ETAYFILKL.
- The dominant response to this HLA allele was to this epitope in 2 of the 3/12 HEPS cases and in all 9/11 HIV-1 infected women that responded to the epitope.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A\*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.
- Subject ML 1203 started with CTL responses to A\*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A\*6802 ETAYFILKL which became dominant, B7 TPGPG(V/I)RYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.
- Subject ML 1707 started with a CTL response to A\*6802 DTVLEDINL prior to seroconversion, and switched to A\*6802 ETAYFILKL and A24 RDYVDRFFKTL post-seroconversion.
- Subject ML 1830 made no detectable response prior to seroconversion, but responded to A\*6802 DTVLEDINL and A\*6802 ETAYFILKL post-seroconversion.

**HXB2 Location** Integrase (96–104)**Author Location** Pol (744–752)**Epitope** ETAYFILKL**Immunogen** HIV-1 infection**Species (MHC)** human (A\*6802)**References** Appay *et al.* 2000

- This epitope is newly defined in this study.
- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.



- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$

**HXB2 Location** Integrase (101–111)

**Author Location** (C consensus)

**Epitope** ILKLAGRWPVK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** epitope processing, rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in a residue outside of the optimized epitope of ILKLAGRWPVK are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** Integrase (105–121)

**Author Location** (C consensus)

**Epitope** AGRWPVKVIHTDNGSNF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5301)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Integrase (123–131)

**Author Location**

**Epitope** STTVKAACW

**Epitope name** SW9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather

than IFN-gamma responses, showed better correlation with the plasma viral variants.

- HLA-B\*57-restricted optimal epitope STTVKAACW was tested for immune response.

**HXB2 Location** Integrase (123–132)

**Author Location** Integrase (123–132)

**Epitope** STTVKAACWW

**Immunogen**

**Species (MHC)** human (B57)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Integrase (123–132)

**Author Location** Integrase

**Epitope** STTVKAACWW

**Epitope name** SW10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** epitope processing, supervised treatment interruptions (STI), rate of progression, immunodominance

**References** Rodriguez *et al.* 2004

- Protease and integrase are shown to be frequently targeted by CD8 T-cell responses (23% and 68% of 56 HIV+ patients, respectively). Responses tend to cluster in conserved regions of Int, although 1 high conserved region had no responses. CTL frequencies per unit protein length for Pro and Int were similar to other HIV non-structural proteins. Three novel HLA class I-restricted optimal epitopes were found and characterized with fine mapping.
- All 5 HLA-B57 patients recognized this epitope and were long-term nonprogressors.

**HXB2 Location** Integrase (123–132)

**Author Location** Pol

**Epitope** STTVKAACWW

**Epitope name** SW10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Two escape mutations, at positions 2 and 3, were found in the most polymorphic residue in the epitope. These were shared between clades B and C. The T840N mutation at residue 2,

sNtvkaacww, was significantly more common in persons expressing HLA-B57, often in conjunction with T841A or V sT[A/V]kaacww.

**HXB2 Location** Integrase (123–132)

**Author Location** Integrase

**Epitope** STTVKAACWW

**Epitope name** B57-SW10(Int)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Integrase (123–132)

**Author Location**

**Epitope** STTVKAACWW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** responses in children, mother-to-infant transmission, characterizing CD8+ T cells

**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

**HXB2 Location** Integrase (127–135)

**Author Location** Pol (869–877)

**Epitope** KAACWWAGI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

**HXB2 Location** Integrase (135–143)

**Author Location** (C consensus)

**Epitope** IQQEFGIPY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the Q2 residue of IQQEFGIPY are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** Integrase (135–143)

**Author Location**

**Epitope** IQQEFGIPY

**Immunogen**

**Species (MHC)** human (B\*1503)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B\*1503 epitope.

**HXB2 Location** Integrase (135–143)

**Author Location** Integrase (135–143)

**Epitope** IQQEFGIPY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Assay type** Other

**Keywords** HLA associated polymorphism

**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in

most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.

- IQQEFGIPY was a previously defined B\*1503 presented epitope that encompassed a polymorphism, IqQEFGIPY, in the second position.

**HXB2 Location** Integrase (135–143)

**Author Location** Integrase

**Epitope** IQQEFGIPY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, rate of progression, immunodominance

**References** Frahm *et al.* 2006

- CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects in spite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- IQQEFGIPY of clade C is a potential HLA-B\*1503-restricted epitope.

**HXB2 Location** Integrase (136–143)

**Author Location** Integrase

**Epitope** KQEFGIPY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, rate of progression, immunodominance

**References** Frahm *et al.* 2006

- CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects in spite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- KQEFGIPY of clade B is a potential HLA-B\*1503-restricted epitope.

**HXB2 Location** Integrase (157–166)

**Author Location** (C consensus)

**Epitope** ELKKIIGQVR

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*33)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- ELKKIIGQVR is an optimal epitope.

**HXB2 Location** Integrase (157–166)

**Author Location** Integrase

**Epitope** ELKKIIGQVR

**Epitope name** ER9

**Immunogen**

**Species (MHC)** human (A\*3301)

**References** Zimbwa *et al.* 2007

- E169D is a processing mutation for HLA-B\*0702 restricted SPAIFQSSM (SM9) as well as an epitope variation for HLA-A\*0301 restricted MTKILEPFR (MR9).
- CTL recognition of Int epitope ELKKIIGQVR was not detected post-infection with either wild type (169E) or mutant 169D HIV-1. ER9 was used as a negative control since Jurkat cell line E6-1 is negative for ER9-restricting HLA-A\*3301.

**HXB2 Location** Integrase (164–172)

**Author Location** (C consensus)

**Epitope** QVRDQAEHL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- QVRDQAEHL is an optimal epitope.

**HXB2 Location** Integrase (165–172)

**Author Location** Integrase (165–172)

**Epitope** VRDQAEHL

**Epitope name** VL8

**Immunogen**

**Species (MHC)** human (Cw\*18)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a Cw18 epitope.

**HXB2 Location** Integrase (165–172)

**Author Location** (C consensus)

**Epitope** VRDQAEHL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*1801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- VRDQAEHL is an optimal epitope.

**HXB2 Location** Integrase (165–172)

**Author Location** Integrase (165–172)

**Epitope** VRDQAEHL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*1801)

**Assay type** Other

**Keywords** HLA associated polymorphism

**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- VRDQAEHL was a previously defined Cw1801 presented epitope that encompassed a Cw18 associated polymorphism, VRdQAEHL, in the third position.

**HXB2 Location** Integrase (165–172)

**Author Location** Integrase (165–172)

**Epitope** VRDQAEHL

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (Cw\*1801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** optimal epitope

**References** Honeyborne *et al.* 2006

- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B\*3910, B\*4201, B\*8101 and Cw\*1801, by motif inference. HLA-A\*2902 was found to overlap those of A1 and A24 supertypes.
- VRDQAEHL was the optimal epitope for HLA-Cw\*1801 with variants VRDQAEH, RDQAEHL, VRDQAEHLk, qVRDQAEHL having been tested.

**HXB2 Location** Integrase (171–180)

**Author Location** Pol

**Epitope** HLKTAVQMAV

**Epitope name** 1247

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A01, A02, B08, Cw16

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for HLKTAVQMAV: 82%

**HXB2 Location** Integrase (173–181)

**Author Location**

**Epitope** KTAVQMAVF

**Epitope name** KF9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B\*57-restricted optimal epitope KTAVQMAVF was tested for immune response.

**HXB2 Location** Integrase (173–181)

**Author Location** Integrase (173–181)

**Epitope** KTAVQMAVF

**Epitope name** intKF9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Country** United Kingdom, Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** TCR usage, structure, characterizing CD8+ T cells

**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFN-PEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** Integrase (173–181)

**Author Location** Pol (888–896)

**Epitope** KTAVQMAVF

**Immunogen**

**Species (MHC)** human (B\*5701)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5701 epitope.

- Epitope is motif based, personal communication from C. Hay.
- Subtype of B57 not determined.

**HXB2 Location** Integrase (173–181)

**Author Location** Pol (888–896)

**Epitope** KTAVQMAVF

**Immunogen**

**Species (MHC)** human (B57)

**References** Hay 1999

- Epitope is motif based, personal communication from C. Hay.

**HXB2 Location** Integrase (173–181)

**Author Location** Pol

**Epitope** KTAVQMAVF

**Epitope name** KF9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was quite conserved in people carrying B57, but two substitutions were found in 11 B57+ individuals tested: Rtavqmaf and ktavqmafL.

**HXB2 Location** Integrase (173–181)

**Author Location** Pol (889–897)

**Epitope** KTAVQMAVF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Integrase (173–181)

**Author Location**

**Epitope** KTAVQMAVF

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** Integrase (173–181)

**Author Location**

**Epitope** KTAVQMAVF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

**HXB2 Location** Integrase (177–186)

**Author Location** Pol (919–928)

**Epitope** QMAVFIHNFK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 5/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** Integrase (178–186)

**Author Location** Pol (920–928)

**Epitope** MAVFIHNFK

**Immunogen** HIV-1 infection**Species (MHC)** human (A3 supertype)**Keywords** supertype, rate of progression**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** Integrase (179–187)**Author Location** Integrase (179–187)**Epitope** AVFIHNFKR**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, AVFIHNFKR, was predicted to be restricted by HLA A\*0301, A\*1101, A\*3101, A\*3301, A\*6601 and A\*6801.

**HXB2 Location** Integrase (179–187)**Author Location** Pol (921–929)**Epitope** AVFIHNFKR**Immunogen** HIV-1 infection**Species (MHC)** human (A3 supertype)**Keywords** supertype, rate of progression**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.

- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 5/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** Integrase (179–188)**Author Location** Integrase (179–188)**Epitope** AVFIHNFKRK**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Keywords** optimal epitope**References** Frahm *et al.* 2008**HXB2 Location** Integrase (179–188)**Author Location** Integrase (179–188)**Epitope** AVFIHNFKRK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*11)**Country** China**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other**Keywords** assay standardization/improvement, optimal epitope**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This putative epitope, AVFIHNFKRK, was detected and confirmed within overlapping peptides AVFIHNFKRKGGIG-GYSA and RKGIGGYSAGERIVDII.

**HXB2 Location** Integrase (179–188)**Author Location** Integrase (179–188 LAI)**Epitope** AVFIHNFKRK**Subtype** B**Immunogen****Species (MHC)** human (A\*1101)**Keywords** optimal epitope**References** Frahm *et al.* 2008; Fukada *et al.* 1999

- C. Brander notes this is an A\*1101 epitope.

**HXB2 Location** Integrase (179–188)**Author Location** Pol (894–903)**Epitope** AVFIHNFKRK**Subtype** B, CRF01\_AE**Immunogen** HIV-1 infection**Species (MHC)** human (A\*1101)

**Keywords** subtype comparisons

**References** Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A\*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A\*1101 epitopes was recognized in a clade specific manner. Two other HLA A\*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- AVFIHNFKRK is commonly found in viruses representing subtypes A-E. It was strongly recognized by CTL from 4/7 E clade infected Thai subjects.

**HXB2 Location** Integrase (179–188)

**Author Location** Pol (894–903 93TH253 subtype CRF01)

**Epitope** AVFIHNFKRK

**Epitope name** P894-903

**Subtype** CRF01\_AE

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Bond *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subjects 265 who was HLA A2/A11 and 128 who was HLA A11/A33, and had been predicted to be a possible A11 epitope using Epimer in Bond *et al.* [2001]

**HXB2 Location** Integrase (179–188)

**Author Location** Integrase

**Epitope** AVFIHNFKRK

**Epitope name** A11-AK10(Int)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Integrase (179–188)

**Author Location** Pol

**Epitope** AVFIHNFKRK

**Epitope name** 1264

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11, A3, A68)

**Donor MHC** A01, A68, B15, B40, Cw03; A03, A11, B14, B51, Cw08, Cw13; A25, A68, B18, B27

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, supertype, computational epitope prediction, immunodominance, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC superotypes.
- Estimated binding probability for AVFIHNFKRK:53% Super-type epitope binding to A11, A03 and A68. Immunodominant.

**HXB2 Location** Integrase (179–188)

**Author Location** Integrase (894–904)

**Epitope** AVFIHNFKRK

**Epitope name** A3-AK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals began to have detectable responses to this epitope after STI.

**HXB2 Location** Integrase (179–188)

**Author Location** Integrase (179–188)

**Epitope** AVFIHNFKRK

**Epitope name** A3-AK10 Pol

**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

- References** Altfeld *et al.* 2002a
- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
  - The second infecting strain had the variant avfVhnfkrk. The CTL response to the second variant was zero at all timepoints. The CTL response to the first variant was low and declined over time.

**HXB2 Location** Integrase (179–188)  
**Author Location** Pol  
**Epitope** AVFIHNFKRK  
**Epitope name** 1264  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A03, A23, B49, B57; A03, A24, B27, B57, Cw13, Cw18

- Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, computational epitope prediction  
**References** De Groot *et al.* 2003
- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
  - Estimated binding probability for AVFIHNFKRK: 52%

**HXB2 Location** Integrase (179–196)  
**Author Location** Pol (894–911)  
**Epitope** AVFIHNFKRKGGIGGYSA  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons  
**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Integrase (185–194)  
**Author Location** Integrase (185–194)  
**Epitope** FKRKGGIGGY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)

**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Integrase (185–194)  
**Author Location** (C consensus)  
**Epitope** FKRKGGIGGY  
**Subtype** C

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004
- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
  - This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Integrase (185–194)  
**Author Location** (C consensus)  
**Epitope** FKRKGGIGGY  
**Subtype** C

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - Mutational patterns in the K4 and G9 residues of FKRKGGIGGY are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** Integrase (185–194)  
**Author Location** Integrase (185–194)  
**Epitope** FKRKGGIGGY  
**Subtype** C

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Assay type** Other  
**Keywords** HLA associated polymorphism  
**References** Boutwell & Essex 2007
- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12%



of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.

- FKRKGGIGGY was a previously defined B\*1503 presented epitope that encompassed a polymorphism, FKRkGGIGGY, in the fourth position.

**HXB2 Location** Integrase (185–194)

**Author Location** Integrase

**Epitope** FKRKGGIGGY

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, rate of progression, immunodominance

**References** Frahm *et al.* 2006

- CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects in spite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- FKRKGGIGGY of clades B and C is a potential HLA-B\*1503-restricted epitope.

**HXB2 Location** Integrase (197–204)

**Author Location** Integrase (196–203)

**Epitope** GERIVDII

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, GERIVDII, of unknown HLA restriction, was detected within overlapping peptides RKGIGGYSAGERIVDII, SAGERIVDIIATDIQTK and DIIATDIQTKELQKQITK.

**HXB2 Location** Integrase (203–211)

**Author Location** Integrase (202–212)

**Epitope** IIATDIQTK

**Epitope name** IK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This novel epitope, IIATDIQTK (IK9), was detected and confirmed within overlapping peptides SAGERIVDIIATDIQTK and DIIATDIQTKELQKQITK.

**HXB2 Location** Integrase (203–211)

**Author Location**

**Epitope** IIATDIQTK

**Epitope name** IK9

**Immunogen**

**Species (MHC)** human (A1101)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a A1101 epitope.

**HXB2 Location** Integrase (210–227)

**Author Location** Pol (925–942)

**Epitope** TKELQKQI I KIQNFRVYY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Integrase (218–227)

**Author Location** Integrase

**Epitope** TKIQNFRVYY

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, rate of progression, immunodominance

**References** Frahm *et al.* 2006

- CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects in spite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- TKIQNFRVYY of clade B is a potential HLA-B\*1503-restricted epitope, with epitope iKIQNFRVYY found in clade C.

**HXB2 Location** Integrase (218–235)

**Author Location** RT-Integrase (218–235 HXB2)

**Epitope** TKIQNFRVYYRDSRPLW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 21% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** Integrase (219–226)

**Author Location** (C consensus)

**Epitope** KIQNFRYY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the K1 residue of KIQNFRYY are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** Integrase (219–227)

**Author Location**

**Epitope** KIQNFRVYY

**Epitope name** Pol-KY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Donor MHC** A\*0205, A\*3002, B\*1402, B\*5301, Cw\*0401, Cw\*0802

**Keywords** HAART, ART

**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Patient 00RCH28 was African American, not on HAART, had a viral load of 5900 and CD4 count of 889, and she also recognized RIRQGLERA, gp160(846-854), A\*0205.
- Among HIV+ individuals who carried HLA A30, 6/16 (38%) recognized this epitope.

**HXB2 Location** Integrase (219–227)

**Author Location** Integrase (219–227)

**Epitope** KIQNFRVYY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Integrase (219–227)

**Author Location** (C consensus)

**Epitope** KIQNFRVYY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Integrase (219–227)

**Author Location** Integrase (219–227)

**Epitope** KIQNFRVYY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, KIQNFRVYY, was predicted to be restricted by HLA A1 and A\*3002.

**HXB2 Location** Integrase (219–227)

**Author Location** Integrase

**Epitope** KIQNFRVYY

**Epitope name** KLY9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Country** South Africa

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization

**Keywords** rate of progression

**References** Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer A\*3002 KLY9 was used to test 20 patients and gave a median ex vivo tetramer frequency of 0.45.

**HXB2 Location** Integrase (219–227)

**Author Location** Integrase (219–227)

**Epitope** KIQNFRVYY

**Epitope name** KIY9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**Country** South Africa

**Assay type** proliferation, Tetramer binding, Intracellular cytokine staining

**References** Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

**HXB2 Location** Integrase (219–227)

**Author Location** Integrase

**Epitope** KIQNFRVYY

**Epitope name** KY9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A30)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** epitope processing, supervised treatment interruptions (STI), immunodominance

**References** Rodriguez *et al.* 2004

- Protease and integrase are shown to be frequently targeted by CD8 T-cell responses (23% and 68% of 56 HIV+ patients, respectively). Responses tend to cluster in conserved regions of Int, although 1 high conserved region had no responses. CTL frequencies per unit protein length for Pro and Int were similar to other HIV non-structural proteins. Three novel HLA class I-restricted optimal epitopes were found and characterized with fine mapping.

**HXB2 Location** Integrase (219–227)

**Author Location**

**Epitope** KIQNFRVYY

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A\*2501, A\*3002; B\*0702, B\*1801

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Integrase (219–227)

**Author Location**

**Epitope** KIQNFVYYY

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120 boost, polyepitope *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human

**Donor MHC** A\*3001, A\*3002; B\*4201/02, B\*4403/26/30

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85–86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Integrase (219–228)

**Author Location** Pol (934–943 SF2)

**Epitope** KIQNFVYYR

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (A\*3303)

**Assay type** Chromium-release assay

**Keywords** binding affinity, computational epitope prediction

**References** Hossain *et al.* 2003

- HLA-A\*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A\*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A\*3303. Six of these served as peptide-targets for lysis by PBMC from infected individual, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
- This epitope is one of the 4 that are properly processed.

**HXB2 Location** Integrase (219–228)

**Author Location** Pol (919–928)

**Epitope** KIQNFVYYR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.

- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 5/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** Integrase (241–249)

**Author Location** Pol (576–584)

**Epitope** LLWKGEAV

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A\*0201)

**References** van der Burg *et al.* 1996

- Slow dissociation rate, associated with immunogenicity in transgenic HLA-A\*0201/K<sup>b</sup> mice.
- CTL generated by *in vitro* stimulation of PBMC derived from uninfected individual.

**HXB2 Location** Integrase (241–249)

**Author Location** RT (956–964 HXB2R)

**Epitope** LLWKGEAV

**Epitope name** LR28

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG

**Species (MHC)** mouse (A\*0201)

**Keywords** binding affinity, vaccine-specific epitope characteristics, immunodominance

**References** Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRFVVTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a strong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

**HXB2 Location** Integrase (241–249)

**Author Location** RT (956–964 HXB2R)

**Epitope** LLWKGEAV

**Epitope name** LR28

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade LAI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12, P30

**Species (MHC)** mouse (A\*0201)

**Keywords** vaccine-specific epitope characteristics, immunodominance

**References** Peter *et al.* 2002

- When HIV-1 peptides were used to vaccinate HLA-A2.1 transgenic A2-Kb mice, strong responses to five peptides were observed when the peptides were given individually, but immunodominance limited the response to some of the peptides when they were given in combination Peter *et al.* [2001]. IL-12 can counteract immunodominance in BALB/c mice, so it was given with the multiple epitope vaccination, and was instead found to specifically eliminate the HLA-A2.1-epitope CTL responses, but not Kb CTL responses. This was possibly a consequence of transient depletion of T-cells, B cells and macrophages in the spleen.

**HXB2 Location** Integrase (241–249)

**Author Location** Pol

**Epitope** LLWKGEAV

**Epitope name** L9V

**Immunogen** vaccine

*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140ΔV3

**Species (MHC)** transgenic mouse (A\*0201)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells

**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** Integrase (241–249)

**Author Location** RT (241–249)

**Epitope** LLWKGEAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.

- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, LLWKGEAV, was predicted to be restricted by HLA A\*0201, A\*0204, A\*0205 and A\*0209.

**HXB2 Location** Integrase (241–249)

**Author Location** Pol (956–964)

**Epitope** LLWKGEAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** dendritic cells

**References** Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.
- 1/6 showed increased Env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.
- LLWKGEAV is a conserved HLA-A2 epitope included in this study – 6/6 patients had this sequence as their HIV direct sequence, but only four of these had a detectable CTL response.

**HXB2 Location** Integrase (241–249)

**Author Location** Pol (956–964 HXB2R)

**Epitope** LLWKGEAV

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (A2)

**References** Parker *et al.* 1992; Parker *et al.* 1994

- Studied in the context of HLA-A2 peptide binding.

**HXB2 Location** Integrase (241–249)

**Author Location** Pol (956–964 HXB2R)

**Epitope** LLWKGEAV

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (A2)

**References** Brander *et al.* 1995

- No CTL activity found in HIV-infected subjects, epitope studied in the context of inclusion in a synthetic vaccine.

**HXB2 Location** Integrase (241–249)

**Author Location** Pol (956–964)

**Epitope** LLWKGEAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A2)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** Integrase (258–275)

**Author Location** RT

**Epitope** KVVPRRKAIIIRDYQKQM

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human**Country** Barbados, Haiti, United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other**Keywords** binding affinity, immunodominance**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J. Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, KVVPRRKAKIIRDYQKQM, had an overall frequency of recognition of 15.3% - 20.3% AA, 7.7% C, 9.1% H, 19% WI.

**HXB2 Location** Integrase (260–268)**Author Location** Integrase (260–268)**Epitope** VPRRKVKII**Subtype C****Immunogen** HIV-1 infection**Species (MHC)** human (B\*42)**Assay type** Other**Keywords** epitope processing, HLA associated polymorphism**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms

were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.

- VPRRKVKII was a previously defined B\*42 presented epitope that was associated with a polymorphism, VPRRKVKIIk seen just after the last position in that epitope.

**HXB2 Location** Integrase (260–268)**Author Location** Integrase (260–268)**Epitope** VPRRKAKII**Immunogen****Species (MHC)** human (B42)**Keywords** optimal epitope**References** Frahm *et al.* 2008**HXB2 Location** Integrase (263–271)**Author Location** Integrase (263–271)**Epitope** RKAKIIRDY**Immunogen** HIV-1 infection**Species (MHC)** human (B\*1503)**Keywords** optimal epitope**References** Frahm *et al.* 2008**HXB2 Location** Integrase (263–271)**Author Location** Integrase (263–271)**Epitope** RKAKIIRDY**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (B\*1503)**Donor MHC** A\*2301, B\*1503, B\*3501, Cw2, Cw7**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** binding affinity, acute/early infection, early-expressed proteins**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** Integrase (263–271)**Author Location** (C consensus)**Epitope** RKAKIIRDY**Subtype C**

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004
- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
  - This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.
- HXB2 Location** Integrase (263–271)  
**Author Location** (C consensus)  
**Epitope** RKAKIIRDY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** epitope processing, rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - Mutational patterns in the A3 residue of RKAKIIRDY are associated with the presence of the HLA presenting molecule in the host. Mutation of a residue outside of the optimized epitope also associated with HLA.
- HXB2 Location** Integrase (263–271)  
**Author Location** Integrase  
**Epitope** RKAKIIRDY  
**Subtype** B, C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, rate of progression, immunodominance  
**References** Frahm *et al.* 2006
- CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects in spite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.

- RKAKIIRDY of clade B is a potential HLA-B\*1503-restricted epitope, with epitope RKAKIIRDY found in clade C.

**HXB2 Location** Integrase (263–271)

**Author Location** Integrase

**Epitope** RKAKIIRDY

**Epitope name** B15-RY9(Int)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Integrase (266–273)

**Author Location** Integrase (266–272)

**Epitope** KIIRDYGGK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, KIIRDYGGK, of unknown HLA restriction, was detected within overlapping peptides KVVPRRKAKIIRDYGGKQM and KIIRDYGGKQMAGDDCVA.

**HXB2 Location** Integrase (266–275)

**Author Location** (C consensus)

**Epitope** KIIKDYGGKQM

**Subtype C****Immunogen** HIV-1 infection**Species (MHC)** human (B\*4201)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the I3 residue of KIIKDYGKQM are associated with the presence of the HLA presenting molecule in the host.
- KIIKDYGKQM not optimized.

**HXB2 Location** Integrase (266–275)**Author Location** Integrase (266–275)**Epitope** KIIKDYGKQM**Epitope name** KM10**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*4201)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction

**II-B-15 Pol CTL/CD8+ epitopes****HXB2 Location** Pol**Author Location****Epitope****Immunogen** computer prediction**Species (MHC)** (A\*0201, B\*3501)**Keywords** subtype comparisons, computational epitope prediction**References** Schönbach *et al.* 2002

- Computational methods (artificial neural networks, hidden Markov models, binding matrices based on HLA association rates) were used to identify HLA-A\*0201 and HLA-B\*3501 HIV T-cell epitope candidates from 533 Gag, Env and Pol sequences of which 374 were derived from HIV-1, 97 were derived from HIV-2 and 62 from SIV. Comparisons to known epitopes and between clades were made.

**HXB2 Location** Pol**Author Location** Pol**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201, Cw\*08)**References** Shacklett *et al.* 2000

- HIV-1 specific, MHC class I-restricted CTL killing was detected in duodenal and rectal gut associated lymphoid tissue (GALT) sites from three infected individuals – the distribution of class I restricted CTL was different in the peripheral blood samples and GALT samples.

**HXB2 Location** Pol**Author Location** RT (IIIB)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Keywords** epitope processing, escape**References** Moore *et al.* 2002b

- HIV polymorphisms in the RT protein were examined relation to HLA alleles found in a population of 473 participants in the Western Australian HIV Cohort Study. 64 significant associations between polymorphisms at particular positions and HLA alleles were detected, for HLA-B7, -B12, -B35 and -B15. Fifteen of these were in positions with known epitopes, 4 in anchor residues, 11 in other positions. Six additional polymorphic sites associated with particular HLA molecules flanked known epitopes and may relate to processing.
- 25 negative associations were also found between polymorphism and HLA alleles. The authors propose this is due to escape mutations in epitopes presented by common HLA types dominating in the population, and give examples of five amino acids which are in the consensus and tend to be stable in those with the most common HLA allele, HLA-A2.

**HXB2 Location** Pol**Author Location** Pol**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Assay type** Tetramer binding, Flow cytometric T-cell cytokine assay**Keywords** assay standardization/improvement**References** Wu *et al.* 2005

- A flow cytometric assay for validation of HIV-1 gag- or pol-specific- CD8/HLA-A2 T-cells was shown to be sensitive and specific, being able to detect HIV-1 CTL at the single T-cell level. An inverse correlation between HIV plasma viremia and gag- and pol-specific-CD8/HLA-A2 T-cells was observed.

**HXB2 Location** Pol



**Author Location** Pol**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*35)**Keywords** rate of progression**References** Jin *et al.* 2002

- Patients with HLA-B\*35 variants B\*3502, B\*3503, B\*3504, and B\*5301 tend to proceed to AIDS more quickly than those with B\*3501.
- Of 32 patients with HLA-B\*35 alleles CD8+ CTL responses were quantified using an intracellular cytokine staining assay – 75% had responses to Pol, 69% to Gag, 50% to Nef, and 41% to Env.
- The overall magnitude of CTL responses did not differ between those bearing B\*3501 and the others. A higher percentage of Gag responses was observed in those that had lower RNA levels that carried B\*3501, and there was a negative association with viral load and CTL activity. The data is consistent with higher levels of CTL responses contributing to protection in B\*3501 individuals, but not in B\*3502, B\*3503, B\*3504, and B\*5301 individuals.

**HXB2 Location** Pol**Author Location** Pol**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade HXB2, B clade NL43 *HIV component:* Gag, Pol**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Huang *et al.* 2001

- Different HIV strains were used for different regions: gag HXB2, pol NL43
- Mice were immunized with four humanized DNA constructs: GagPol, that would form a pseudoparticle carrying Gag and Pol, Gag, Pol or a GagPol fusion construct.
- The GagPol pseudoparticle, Gag and GagPol fusion construct all elicited strong anti-Gag CTL, but only the GagPol fusion construct elicited strong anti -Pol CTL.

**HXB2 Location** Pol**Author Location** RT (LAI)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Buseyne *et al.* 1998a

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load.

**HXB2 Location** Pol**Author Location** p66 (LAV)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** epitope processing, dendritic cells**References** Zheng *et al.* 1999

- Protein delivery (gp160 LAV, p66 LAV, and p24 NY5) to human dendritic cells (DC) with liposomes provides enhanced memory CTL response relative to delivery of protein alone.
- Chloroquine administration enhanced epitope presentation, and brefeldin A and peptide aldehyde inhibitors inhibited antigen presentation, suggesting epitopes were processed by classical proteasome pathway.

**HXB2 Location** Pol**Author Location** Pol (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression, Th1**References** Wasik *et al.* 2000

- HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of beta-chemokines and IL-2 relative to other HIV+ infants.
- No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors.
- CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccina/HIV constructs.

**HXB2 Location** Pol**Author Location** Pol (LAI)**Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp41, Protease, V3**Species (MHC)** human**References** Salmon-Ceron *et al.* 1999

- The vaccine used was a rec canarypox with HIV-1 gp120 MN, tm/gag/protease LAI (vCP205), alone or with p24E-V3 MN synthetic peptide (CLTB-36))
- Twenty HIV negative subjects were vaccinated in phase I trial with combinations of vCP205 and CLTB-36.
- Immunization with vCP205 induced HIV-1-specific ABs to gp120, V3, and p24 antigens, and CTL immune responses against vCP205 were detected after the fourth immunization in 33% of the subjects against Env, Gag and Pol, but the CLTB-36 peptide did not produce AB or CTL immune responses against p24 or gp160.

**HXB2 Location** Pol**Author Location** Pol (172–219 subtype B)**Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade SF2 *HIV component:* Env, Gag, Nef, Protease**Species (MHC)** human**References** Gorse *et al.* 1999b

- The vaccine used was rec canarypox expressing HIV-1 env, gag, pol, nef and protease (vCP300) with or without administration of HIV-1 SF-2 rgp120.

- In vitro inducible CTL activity against HIV-1 Env, Gag, Pol, and Nef antigens was observed in 79% (15 of 19) of vaccine recipients.
- The combination of vCP300 and vP1291 together resulted in an overall increase in CTL induction and detection sensitivity.

**HXB2 Location** Pol**Author Location** Pol (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression**References** Betts *et al.* 1999

- This study demonstrated an inverse correlation between HIV Type I plasma viral load and CTL activity directed against HIV-1 Pol, and stronger combined effects of Pol- and Env-specific CTL, in long-term survivors (LTS) of HIV-1 infection.

**HXB2 Location** Pol**Author Location** Pol (BRU)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression**References** Aladdin *et al.* 1999

- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death.

**HXB2 Location** Pol**Author Location** RT (LAI)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Buseyne *et al.* 1998b

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes.

**HXB2 Location** Pol**Author Location** RT**Epitope****Immunogen** vaccine*Vector/Type:* DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12**Species (MHC)** mouse**References** Kim *et al.* 1997c

- A gag/pol, vif or gp160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice.
- When IL-12 was present, CTL response could be detected even without *in vitro* stimulation.

**HXB2 Location** Pol**Author Location** RT**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Trickett *et al.* 1998

- Twelve HIV-1 infected patients were re-infused with their own lymphocytes, cryopreserved from an earlier time point in the infection.
- Improvement in CD4+ and CD8+ T cells were seen in 7/12, and an increase in the CTL response to Pol was seen in one patient.

**HXB2 Location** Pol**Author Location** RT**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression**References** Froebel *et al.* 1997

- Two HIV-1 infected children with contrasting disease courses were followed longitudinally – one died of AIDS, the other is a long-term non-progressor.
- Reactivity against Gag, Pol, Env and Tat proteins was tested by PBMC bulk cultured cells reacting with protein expressed in vaccinia constructs in autologous EBV transformed B cells.
- The child who progressed consistently had CTL against Pol and Tat.
- The long-term non-progressing child had no detectable CTL, but was heterozygous for a mutation in the CCR5 receptor and for HLA-B49, which has been shown to be associated with slower progression.

**HXB2 Location** Pol**Author Location** Pol (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Betts *et al.* 1997

- 6/8 individuals from Zambia infected with C clade virus had CTL that were able to make response to B clade HIV-1 IIIB vaccinia-expressed Gag, Pol and Env proteins.
- A vigorous cross-clade response was not limited to a particular protein, and the level of recognition of different proteins varied among the six patients.

**HXB2 Location** Pol**Author Location** RT**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** De Maria *et al.* 1997

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T cell function.
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels.

**HXB2 Location** Pol**Author Location** Pol (LAI, MN)

**Epitope****Immunogen** HIV-1 exposed seronegative**Species (MHC)** human**References** Goh *et al.* 1999

- 13/37 exposed uninfected individuals with repeated high-risk sexual exposure had HIV-1 specific CTL against Env, Gag, Pol, or a combination of proteins – CTL activity was correlated with a CCR5 wildtype genotype.
- In this group, the highest CTLp frequencies were directed at Gag, but the most common response was to Env and four individuals had responses to multiple HIV-1 proteins.

**HXB2 Location** Pol**Author Location** Pol (LAI)**Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* canarypox *HIV component:* Gag, gp120, gp41, Nef, Protease, RT**Species (MHC)** human**References** Evans *et al.* 1999

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination.

**HXB2 Location** Pol**Author Location** Gag/Pol (MN)**Epitope****Immunogen** vaccine*Vector/Type:* DNA *HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86**Species (MHC)** chimpanzee**References** Kim *et al.* 1998

- The study explores the use of co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

**HXB2 Location** Pol**Author Location** Pol (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Jin *et al.* 1998a

- CTL precursor frequencies were determined in HIV-1 infected pregnant women, and significantly higher CTLp frequencies to Pol and Nef were found in non-transmitting mothers than in transmitting mothers;

**HXB2 Location** Pol**Author Location** Pol**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Young *et al.* 2001

- Addition of recombinant rec human IL12 (rhIL12) to cultures increased HIV-specific lysis of HIV-Gag, Pol and gp120 vaccinia expressed antigens (11/15 tested increased lysis by > 5%) if the culture was derived from HIV+ individuals who had CD4 cells/ul > 500.
- 2/10 individuals with <200 CD4 cells/ul, and 3/10 individuals with 200-500 CD4cells/ul, had an increase of >5% upon treatment of the culture with rhIL12, so a few individuals in late stage disease had CD8 cells that maintained responsiveness to rhIL12.

**HXB2 Location** Pol**Author Location** RT (subtype A, B, D)**Epitope****Subtype** A, B, D**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.

**HXB2 Location** Pol**Author Location** Pol**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** White *et al.* 2001

- HIV-specific CTL activity was detected in the female reproductive tract of only 1/3 HIV-infected women who underwent a hysterectomy, although CTL could be identified in the PBMC of all three women.

**HXB2 Location** Pol**Author Location** Pol (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression**References** Jin *et al.* 2000a

- The CTL precursor level (CTLp) was measured in long term non-progressors (LTNP) with low viral load using limiting dilution analysis and measuring CTL against Env Gag and Pol expressed in vaccinia in autologous targets.
- LTNPs have high memory CTL numbers and low viral load.

**HXB2 Location** Pol**Author Location** Pol**Epitope****Immunogen** HIV-1 exposed seronegative**Species (MHC)** human

**Keywords** review, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 2001

- This is a review that summarizes observations about HIV-specific CTL found in the HIV-1 exposed persistently seronegative (HEPS) population.
- The CTL responses assayed by ELISPOT and by CTL precursor frequencies by limiting dilution analysis indicate that CTL in HEPS individuals tend to be of a lower magnitude than in chronic HIV-1 infections – the responses in HEPS cases are below the level of detection by tetramer assays.
- CD8+ CTL responses tend to be detectable in HEPS subjects only if they are recently exposed, and the response diminishes if exposure is reduced – it is not clear if there is a stable memory population in HEPS cases.
- CD8+ CTL responses in the HEPS population are associated with HIV-1 specific CD4+ T cell responses, assayed by proliferation assays, IL-2 secretion, and ELISPOT, and the authors consider the possibility that HIV-1-specific T-help responses improve the "quality" of the CD8+ response in HEPS individuals relative to HIV-1 infected individuals, who tend to have a poor HIV-1-specific T-help response.
- HIV-1 specific CD8+ CTL responses in HIV-1 infected individuals show reduced levels of perforin, and the T cells may not mature properly, and although similar studies have not been conducted in HEPS individuals this is considered as a possible difference in the CTL immune response in HEPS and HIV-1 infected people.

**HXB2 Location** Pol

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission

**References** De Maria *et al.* 1994; Kuhn *et al.* 2002

- 6/24 HIV uninfected infants (ages 15-50 months) born to HIV+ mothers had HIV-1 specific CTL responses to vaccinia-expressed Nef, Gag/Pol, Env.
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Pol

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission, rate of progression

**References** Kuhn *et al.* 2002; Wasik *et al.* 1999

- In HIV-infected infants HIV-specific, CTL responses were not detectable in icord blood or in PBMC collected shortly after birth and were absent or remained very low in 3 infants with a rapidly progressive disease. For those who progressed more slowly, the HIV-specific CTL activity varied.

- The two infants with high levels of Env peptide-stimulated IL-2 responses had the highest CTLp frequencies.
- Stronger responses were detected after initiation of the antiretroviral therapy.
- Two babies that were not infected though born to HIV+ mothers had detectable though low HIV-specific CTLp responses to Env (1/2), Pol (2/2), Gag (1/2) cord blood and transiently in PBMC after birth.
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Pol

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission

**References** Aldhous *et al.* 1994; Kuhn *et al.* 2002

- Six of nine HIV vertically infected infants had HIV-1 specific CTL responses to vaccinia expressed Tat (4/6), Pol (6/6), Env (1/6), or Gag (1/6), but not all responses were detected at all time points.
- Two of eleven babies that were not infected though born to HIV+ mothers had detectable responses Tat (1/2), Pol (2/2), Gag (1/2).
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Pol

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed; however, epitopes were not found that span the invariant, most highly conserved regions of RT and Protease. This might be due to the virus evolving conserved features that disallow the CTL responses in these most conserved regions, as functional constraints for enzyme function would not tolerate change, and normal capacity for immune escape by rapid evolution is lost in these domains.

**HXB2 Location** Pol

**Author Location**

**Epitope**

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, subtype comparisons

**References** Loemba *et al.* 2002

- Therapeutic RT inhibitors were used to select *in vitro* for resistance mutations in subtype C viruses. Many of the resistance mutations were located within analogs to CTL epitopes that had been defined for the B subtype,

**HXB2 Location** Pol  
**Author Location** (IIIB)  
**Epitope**

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HAART, ART, acute/early infection  
**References** Ortiz *et al.* 2002
- Subjects treated with HAART early in HIV-infection showed a correlation between the number of viremic episodes and the total as well as the Pol-specific CD8 T-cell activity as measured by Elispot SFC per million PBMC summed across Pol, Env, Nef and Gag. The subjects treated early after infection had higher levels of CD8+ T-cell activity (N = 31) than those treated later (N = 23), and a greater capacity to enhance CD8+ T-cell responses to viremic episodes.

**HXB2 Location** Pol  
**Author Location** (MN)  
**Epitope**

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** rate of progression  
**References** Edwards *et al.* 2002
- 96% (26/27) chronically infected HIV-1 infected patients elicited gamma-IFN CD8+ T-cell responses against Gag.
  - Nef and/or Pol CTL responses were detected in 86% of the subjects.
  - The magnitude and breadth of Gag and p24 T-cell responses correlated with absolute CD4 counts, and inversely correlated with viral load.
  - Pol and Int CTL responses correlated positively with absolute CD4+ T-cell count.
  - Nef and Env responses did not correlate with either CD4 counts or viral load.

**HXB2 Location** Pol  
**Author Location**  
**Epitope**

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HAART, ART, dendritic cells  
**References** Larsson *et al.* 2002b
- Autologous mature dendritic cells with rec vaccinia expressing Gag, Pol, Nef and Env could amplify CD8+ T-cell Elispot responses 4-38 fold in five HIV+ patients on successful HAART treatment, relative to autologous monocytes. Some weak responses could only be detected using mature dendritic cells as APCs, and this approach could be useful for detection of low frequency memory cells.

**HXB2 Location** Pol  
**Author Location** (IIIB)  
**Epitope**

- Immunogen** HIV-1 infection  
**Species (MHC)** human

**Keywords** immunotherapy

**References** Trickett *et al.* 2002

- Conditions were optimized for ex-vivo expansion of CD8+ and CD4+ T-cells with the goal of functional T-cell production for autologous immunotherapy. 10,000-fold expansions were obtained in 14 days with optimized concentrations of IL-2, anti-CD3 and anti-CD28 coated microspheres, and decreasing amounts of serum over the first 8 days.

**HXB2 Location** Pol  
**Author Location** (IIIB)  
**Epitope**

- Subtype** B  
**Immunogen** HIV-1 and HCV co-infection  
**Species (MHC)** human  
**Keywords** rate of progression  
**References** Lauer *et al.* 2002
- HIV-1 and HCV immune responses were studied in 22 individuals who were co-infected with HIV-1 and hepatitis C virus (HCV). IFN $\gamma$  production was measured in an Elispot assay of CD8+ T-cells using targets expressing either Gag, RT, Env and Nef in a vaccinia construct, or one of seven HCV proteins.
  - All 22 patients targeted at least one protein. 20/22 patients recognized RT, 17/22 patients recognized Gag, 13/22 subjects recognized Env and 11/22 patients recognized Nef. Robust CTL activity was independent of disease progression or viral load.
  - Despite high HCV viral loads, very few HCV CD8+ T-cell Elispot responses were detected. In a control HCV infected person who did not have HIV-1, strong anti-HCV responses were mounted.
  - HIV-specific CD4 proliferative responses were detected in 9/17 coinfecting patients, but no HCV responses were detected.

**HXB2 Location** Pol  
**Author Location**  
**Epitope**

- Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HAART, ART, responses in children  
**References** Scott *et al.* 2001
- CTL responses before and after initiation of ART were studied in 13 HIV-1 vertically infected infants <6 months of age, and 4 that were >6 months of age.
  - Before ART 2/13 infants <6 months of age showed IFN $\gamma$  Elispot CD8+ T-cell responses, one to Nef and one to Env and Nef, and these responses became undetectable after successful therapy– 3 infants were coinfecting with CMV and all 3 had CMV-specific CD8+ T-cell responses.
  - One older infant, at 23 months, had CTL responses against all for proteins tested, Gag, Pol, Nef and Env, and had the lowest plasma viremia of the study group. 3/4 infants older than 6 months of age responded to either Nef or Pol.
  - Administration of ART over 48 weeks broadened the HIV-1-specific CTL response in 2/4 of the older children that were incomplete responders.

**HXB2 Location** Pol

**Author Location** (IIIB, MN)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** dendritic cells**References** Larsson *et al.* 2002a

- Dendritic cells acquire and present HIV-1 antigens derived from dead, apoptotic cells or from non-infectious, fusion-competent HIV-1 virions, and these DC cells could stimulate CD4+ and CD8+ T-cells resulting in IFN $\gamma$  production in an Elispot assay. Both HLA Class I and class II molecules were used for presentation. This may be an important aspect of the initial immune response to HIV-1 infection of CD4+ cells in the mucosal subepithelia.

**HXB2 Location** Pol**Author Location** (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, supervised treatment interruptions (STI)**References** Ortiz *et al.* 2001

- Immune responses in eight chronically HIV-1 infected patients undergoing HAART therapy structured treatment interruptions (STI) were studied. STI boosted HIV-1 specific CTL responses and elevated CTL responses were maintained up to 22 weeks after the last treatment interruption, but viral load rebound to pretreatment levels and CD4 T-cell count decline was observed. CD8 responses in PBMC were measured by cytokine flow cytometry with gp160, Gag p55, RT-Pol and Nef expressed in vaccinia.

**HXB2 Location** Pol**Author Location** Protease-RT**Epitope****Immunogen** SHIV infection, vaccine*Vector/Type:* peptide *HIV component:* Protease, RT**Species (MHC)** macaque**Assay type** Intracellular cytokine staining**Keywords** HAART, ART, vaccine-specific epitope characteristics, vaccine-induced epitopes, escape, immunotherapy**References** Stratov *et al.* 2005

- CD8 T-cells targeting epitopes spanning drug resistance induced mutations were detected in 3/25 individuals harboring multidrug-resistant HIV-1. Novel CD8 T-cell responses were detected against epitopes with common protease inhibitor fitness mutations. T-cell immunity to drug-resistant variants was confirmed in SHIV-infected macaques, where CD8 and CD4 immune responses to RT and protease resistance mutations were elicited using peptide-based immunotherapy.
- The SHIV infected macaques that responded best to the peptide vaccine were those that did not yet have progressive disease. Thus peptide immunotherapy for multidrug resistance has the best hope of success if given to those who are not yet fully immunocompromised.

**HXB2 Location** Pol**Author Location** Pol**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Country** China**Assay type** T-cell Elispot**References** Wang *et al.* 2006

- The association between T cell response and CD4+ T cell counts or CD4+ was investigated, using overlapping peptides corresponding to natural B clade and C consensus sequences.
- T cell responses and CD4+ count were correlated for Gag p24 and Gag p17 (B and C clades) and for Pol (C clade). CD4+ counts were higher in patients with Tat and /or Rev T cell response than in patients without Tat and Rev response.

**II-B-16 Vif CTL/CD8+ epitopes****HXB2 Location** Vif (17–26)**Author Location** (LAI)**Epitope** RIRTWKSLVK**Subtype** B**Immunogen****Species (MHC)** human (A\*0301)**Keywords** optimal epitope**References** Altfeld 2000; Frahm *et al.* 2008**HXB2 Location** Vif (17–26)**Author Location** Vif (17–26 SF2)**Epitope** RIRTWKSLVK**Epitope name** RK10**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**References** Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- 10/29 (35%) individuals tested responded to Vif.
- This epitope was recognized by 3/15 individuals expressing A\*0301 allele.
- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- Overlapping Vif peptides QVDRMRIRTWKSLVK and RIRTWKSLVKHHMYI both reacted with T-cells from AC-06 and contained epitope RIRTWKSLVK.

**HXB2 Location** Vif (17–26)**Author Location** Vif (17–26)**Epitope** RIRTWKSLVK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Keywords** early-expressed proteins**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vif (17–26)

**Author Location**

**Epitope** RIRTWKSLVK

**Epitope name** Vif-RK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A03, 3/21 (14%) recognized this epitope.

**HXB2 Location** Vif (17–26)

**Author Location** Vif (17–26)

**Epitope** RIRTWKSLVK

**Epitope name** A3-RK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Vif (17–26)

**Author Location** Vif (17–26)

**Epitope** RIRTWKSLVK

**Epitope name** A3-RK10 Vif

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant riStwkslvk. The initial CTL response to persisted to against both variants after the superinfection was established.

**HXB2 Location** Vif (17–26)

**Author Location** Vif (17–26)

**Epitope** RIRTWKSLVK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** Vif (17–26)

**Author Location** (B consensus)

**Epitope** RIRTWKSLVK

**Epitope name** RK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A02, A03, B08, B62, Cw10, Cw7; A03, B07, Cw7

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 2/9 individuals recognized this epitope, presented by HLA-A3.

**HXB2 Location** Vif (17–26)

**Author Location** Vif**Epitope** RIRTWKSLVK**Epitope name** RK10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A3)**Donor MHC** A1, A3, B57, B7, Cw6, Cw7**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 6, rirtwNslvk, was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** Vif (17–26)**Author Location** Vif**Epitope** RIRTWKSLVK**Epitope name** A3-RK10(Vif)**Immunogen** HIV-1 infection**Species (MHC)** human (A3)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Vif (17–26)**Author Location****Epitope** RIRTWKSLVK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** epitope processing, escape**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.

- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Vif (23–31)**Author Location** Vif (23–)**Epitope** SLVKHHMYV**Epitope name** Vif23(9V)**Immunogen** HIV-1 infection, vaccine*Vector/Type:* peptide *HIV component:* Vif  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)**Species (MHC)** human, transgenic mouse (A2)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** binding affinity, subtype comparisons, computational epitope prediction**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Response was detected in 1/17 HIV+ HLA-A2 subjects.
- The variant slvkhmyI was an intermediate A2 binder, and stimulated immune responses in fewer A2 transgenic mice. The same person recognized both variants.

**HXB2 Location** Vif (27–41)**Author Location** Vif**Epitope** HHMYISKKAKGWFYR**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** early-expressed proteins**References** Addo *et al.* 2002b



- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot – 33% (23/70) targeted one or more Vif peptides, and this peptide was the most frequently recognized epitope in Vif (25%).
- The regulatory proteins Rev and Tat combined contributed to 3%, and the accessory proteins Vif, Vpr and Vpu to 7%, of the total magnitude of HIV-1 specific CTL responses in a subset of 22 HIV-1 infected individuals in whom all HIV-1 proteins were studied.

**HXB2 Location** Vif (28–36)

**Author Location** Vif (28–36)

**Epitope** HMYISKKAK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vif (28–36)

**Author Location** Vif (28–36)

**Epitope** HMYISKKAK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Vif (28–36)

**Author Location** Vif (28–36)

**Epitope** HMYISKKAK

**Epitope name** A3-HK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.

- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 2/7 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Vif (28–36)

**Author Location** Vif

**Epitope** HMYISKKAK

**Epitope name** A3-HK9(Vif)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Vif (31–39)

**Author Location**

**Epitope** ISKKAKGWF

**Epitope name** IF9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B\*57-restricted optimal epitope ISKKAKGWF was tested for immune response.

**HXB2 Location** Vif (31–39)

**Author Location** Vpr (31–39)

**Epitope** ISKKAKGWF

**Epitope name** vifIF9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Country** United Kingdom, Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** TCR usage, structure, characterizing CD8+ T cells

**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.
- In addition, immunodominance of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFN-PEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** Vif (31–39)

**Author Location** Vif (31–39 SF2)

**Epitope** ISKKAKGWF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**References** Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- 10/29 (35%) individuals tested responded to Vif.
- This epitope was recognized by 2/6 individuals expressing B\*5701 allele.

**HXB2 Location** Vif (31–39)

**Author Location** Vif (31–39)

**Epitope** ISKKAKGWF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vif (31–39)

**Author Location** Vif (31–39)

**Epitope** ISKKAKGWF

**Immunogen**

**Species (MHC)** human (B\*5701)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Vif (31–39)

**Author Location** Vif

**Epitope** VSKKAKGWI

**Epitope name** VI9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 1, Askakwi, was found in the most polymorphic residue in the epitope.

**HXB2 Location** Vif (31–39)

**Author Location** Vif

**Epitope** ISKKAKGWF

**Epitope name** B57-IF9(Vif)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Vif (31–39)

**Author Location**

**Epitope** ISKKAKGWF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

**HXB2 Location** Vif (31–39)

**Author Location**

**Epitope** ISKKAKGWF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Vif (41–57)

**Author Location** (C consensus)

**Epitope** RHHYESRHPKVSSEVHI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1510)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Vif (48–57)

**Author Location** Vif (48–57 SF2)

**Epitope** HPRVSSEVHI

**Epitope name** HI10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**References** Altfield *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- 10/29 (35%) individuals tested responded to Vif.
- This epitope was recognized by 3/8 individuals expressing B\*0702 allele.

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- Overlapping Vif peptides HHYESTHPRVSSEVH and TH-PRVSSEVHIPLG both reacted with T-cells from AC-06 and contained epitope HPRVSSEVHI.

**HXB2 Location** Vif (48–57)

**Author Location** Vif (48–57)

**Epitope** HPRVSSEVHI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vif (48–57)

**Author Location** Vif (48–57)

**Epitope** HPRVSSEVHI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Vif (48–57)

**Author Location** (C consensus)

**Epitope** HPKVSSEVHI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Vif (48–57)

**Author Location** (C consensus)

**Epitope** HPKVSSEVHI

**Subtype C****Immunogen** HIV-1 infection**Species (MHC)** human (B\*4201)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the H1 residue of HPKVSSEVHI are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** Vif (48–57)**Author Location** Vif (48–57)**Epitope** HPKVSSEVHI**Epitope name** HI10**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*4201)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction

**HXB2 Location** Vif (48–57)**Author Location** Vif (48–57)**Epitope** HPRVSSEVHI**Epitope name** B7-HI10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Donor MHC** A3, B7, Cw7**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.

- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Vif (48–57)**Author Location** Vif (48–57)**Epitope** HPRISSEVHI**Epitope name** B7-HM0 Vif**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant hpKissevhi. The CTL response was equal against both variants, and declined over time.

**HXB2 Location** Vif (48–57)**Author Location** (B consensus)**Epitope** HPRISSEVHI**Epitope name** HI10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Donor MHC** A03, B07, Cw7**Country** United States**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** Vif (48–57)**Author Location** (B consensus)**Epitope** HPKISSEVHI

- Epitope name** HKI10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Donor MHC** A03, B07, Cw7  
**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells  
**References** Lichtenfeld *et al.* 2004c
- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
  - 1/9 individuals recognized this epitope.
- HXB2 Location** Vif (48–57)  
**Author Location** Vif  
**Epitope** HPRISSEVHI  
**Epitope name** HI10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Donor MHC** A1, A3, B57, B7, Cw6, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a
- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - One escape mutation, at position 2, hSrissevhi, was found not to correspond to the most polymorphic residue in the epitope.
- HXB2 Location** Vif (48–57)  
**Author Location** Vif  
**Epitope** HPRVSSEVHI  
**Epitope name** B7-HI10(Vif)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
  - The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Vif (48–57)

**Author Location**

**Epitope** HPRVSSEVHI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Vif (54–63)

**Author Location** (C consensus)

**Epitope** EVHIPLGEAR

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the R10 residue of EVHIPLGEAR are associated with the presence of the HLA presenting molecule in the host.

- EVHIPLGEAR not optimized.

**HXB2 Location** Vif (57–66)  
**Author Location** Vif (57–66)  
**Epitope** IPLGDAKLII  
**Immunogen**  
**Species (MHC)** human (B51)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Vif (57–66)  
**Author Location** Vif (57–66)  
**Epitope** IPLGDAKLII  
**Epitope name** II10  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay  
**Keywords** escape, acute/early infection  
**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The peptide that carries this epitope was recognized at high levels early in infection, and the response to this epitope diminished over time. The epitope sequence varied between months 3 and 32.

**HXB2 Location** Vif (61–69)  
**Author Location** Vif  
**Epitope** DAKLIITTY  
**Epitope name** Vif-DY9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*35)  
**Donor MHC** A\*02, A\*03, B\*35, B\*51  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** rate of progression, acute/early infection, memory cells  
**References** Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope DY9, DAKLIITTY, a patient with oscillating ART had IFN-gamma secretion by CD127 lo cells during viremia and CD127hi cell-IFN-gamma production during viremic control. Shortly after ART cessation, CD127 mixed cells secreted IFN-gamma.

**HXB2 Location** Vif (61–69)  
**Author Location** Vif (61–69)  
**Epitope** DAKLIITTY  
**Epitope name** DY9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay  
**Keywords** escape, acute/early infection  
**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- The peptide that carries this epitope was recognized early in infection but the response diminished over time. A point mutation of epitope position 7 (T to K, DAKLIITTY) was detected at high frequency at a chronic infection timepoint, 34 months. The K variant was an escape form, and had low avidity by gamma IFN Elispot.

**HXB2 Location** Vif (61–69)  
**Author Location**  
**Epitope** DAKLVITTY  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN  
*HIV component:* Gag-Pol, gp120, gp41  
**Species (MHC)** human  
**Donor MHC** A2A2; B35, B62  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes  
**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Vif (61–69)  
**Author Location**  
**Epitope** DAKLVITTY  
**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120 boost  
*Strain:* B clade LAI, B clade MN  
*HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Vif (61–80)

**Author Location** Vif (61–80)

**Epitope** EARLVIKTYWGLGTGERDWH

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Vif (64–81)

**Author Location** Vif

**Epitope** LVITTYWGLHTGERDWHL

**Epitope name** VIF-09

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.

- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, LVITTYWGLHTGERDWHL differs from the consensus C sequence LVIKTYWGLqtGERDWHL at 3 amino acid positions, i.e. by 16.7%.

**HXB2 Location** Vif (71–90)

**Author Location** Vif (71–90)

**Epitope** GLQTGERDWHLGHGVSIEWR

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Vif (72–89)

**Author Location** (C consensus)

**Epitope** LQTGERDWHLGHGVSIEW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5703)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Vif (73–81)

**Author Location** Vif (73–81)

**Epitope** HTGERDWHL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35)

**Donor MHC** A\*03, A\*24, B\*35, B\*40

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, variant cross-recognition or cross-neutralization, superinfection

**References** Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- The response to this epitope, HTGERDWHL, was present before superinfection but waned afterward. The epitope from the first strain had the substitution hPgerdwhl, while the second strain matched the test peptide.

**HXB2 Location** Vif (79–87)

**Author Location** Vif (79–87)

**Epitope** WHLGHVSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1510)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Vif (79–87)

**Author Location** Nef (C consensus)

**Epitope** WHLGHGVSI

**Epitope name** WI9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1510)

**Donor MHC** A\*2601, A\*7401, B\*0801, B\*1510, Cw\*0202, Cw\*0801

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** assay standardization/improvement, characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was one of two used to illustrate how specific epitopes were characterized with regard to defining the optimal epitope and the HLA restricting element. HLA allelic associations in the population with peptide recognition was generally high predictive of the epitope within the 15 mer.

**HXB2 Location** Vif (79–87)

**Author Location** (C consensus)

**Epitope** WHLGHGVSI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1510)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Vif (79–87)

**Author Location** (C consensus)

**Epitope** WHLGHGVSI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1510)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** epitope processing, rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the V7 residue of WHLGHGVSI are associated with the presence of the HLA presenting molecule in the host. Mutation of a residue outside of the optimized epitope is also associated with the HLA.

**HXB2 Location** Vif (79–87)

**Author Location** Vif (79–87)

**Epitope** WHLGHGVSI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1510)

**Assay type** Other

**Keywords** epitope processing, HLA associated polymorphism

**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.



- WHLGHGVS I was a previously defined B\*1510 presented epitope that was associated with a polymorphism, dIWHLGHGVS I, in the first position before that epitope. This epitope was embedded in a previously identified CTL immunoreactive region.

**HXB2 Location** Vif (79–87)

**Author Location** Vif (79–87)

**Epitope** WHLGQGVSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3801)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Vif (85–102)

**Author Location** (C consensus)

**Epitope** VSIEWRLRRYSTQVDPGL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*18)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Vif (93–110)

**Author Location** Vif

**Epitope** RYSTQVDPGLADQLIHLY

**Epitope name** VIF-13

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between

clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.

- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, RYSTQVdPGLADQLIHly differs from the consensus C sequence RYSTQVePGLADQLIHmh at 3 amino acid positions, i.e. by 16.7%.

**HXB2 Location** Vif (101–109)

**Author Location** Vif (101–)

**Epitope** GLADQLIHL

**Epitope name** Vif101(9L)

**Immunogen** HIV-1 infection, vaccine, computer prediction

*Vector/Type:* peptide *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder that induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 3/17 HIV+ HLA-A2 subjects.
- The variant gladqlihM was an intermediate A2 binder, but still could stimulate a response in HLA-A2 transgenic mice. It was not recognized by the 3 people who recognized with GLADQLIHL.

**HXB2 Location** Vif (101–110)

**Author Location** Vif

**Epitope** DLADQLIHLY

**Epitope name** 1237

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A02, A30, B39; A01, A02, B08, Cw16

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for DLADQLIHLY: 54%

**HXB2 Location** Vif (102–111)

**Author Location** Vif (102–111 SF2)

**Epitope** LADQLIHLHY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1801)

**References** Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- 10/29 (35%) individuals tested responded to Vif.
- This epitope was recognized by 2/5 individuals expressing B\*1801 allele.

**HXB2 Location** Vif (102–111)

**Author Location** Vif (102–111)

**Epitope** LADQLIHLHY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1801)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vif (102–111)

**Author Location** Vif (102–111)

**Epitope** LADQLIHLHY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1801)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Vif (102–111)

**Author Location** Vif (102–110)

**Epitope** LADQLIHLHY

**Epitope name** LY10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B18)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** optimal epitope

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

**HXB2 Location** Vif (102–111)

**Author Location** Vif (102–110)

**Epitope** LADQLIHLHY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B18)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Vif (102–111)

**Author Location**

**Epitope** LADQLIHLHY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Vif (106–123)

**Author Location** (C consensus)

**Epitope** LIHMHYFDCFADSAIRKA

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Vif (127–135)  
**Author Location** Vif  
**Epitope** HIVSPRCEY  
**Epitope name** HY9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A29)  
**Donor MHC** A28, A29, B14, B44, Cw8  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 3, HIgSPRCEY, was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** Vif (127–135)  
**Author Location** Vif (125–135)  
**Epitope** HIVSPRCEY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** 1261: A\*0201, A29, B58, B62, Cw\*0304, Cw\*1601  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** binding affinity, acute/early infection, early-expressed proteins  
**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** Vif (149–157)  
**Author Location** Vif (149–)  
**Epitope** ALAALITPK  
**Epitope name** Vif149  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* peptide *HIV component:* Vif  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)  
**Species (MHC)** human, transgenic mouse (A2)  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction  
**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.

**HXB2 Location** Vif (151–168)  
**Author Location** (C consensus)  
**Epitope** TALIKPKKIKPPLPSVRK  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*1701)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Vif (158–166)  
**Author Location** Vif (158–)  
**Epitope** KIKPPLPSV  
**Epitope name** Vif158(2I)  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* peptide *HIV component:* Vif  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)  
**Species (MHC)** human, transgenic mouse (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction  
**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CD8+ T-cell IFN gamma responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.
- The substitution kTkpplpsv was also a good binder, but did not elicit a response in transgenic mice, and no response to this variant was detected among the 17 HIV+ people tested.

**HXB2 Location** Vif (158–168)

**Author Location** Vif (158–168)

**Epitope** KTKPPLPSVKK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vif (158–168)

**Author Location** Vif (158–168)

**Epitope** KTKPPLPSVKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Vif (158–168)

**Author Location**

**Epitope** KTKPPLPSVKK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A03)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.

- Epitope KTKPPLPSVKK elicited a magnitude of response of 580 SFC with a functional avidity of 0.05nM and binding affinity of 1.4nM.

**HXB2 Location** Vif (158–168)

**Author Location** (B consensus)

**Epitope** KTKPPLPSVKK

**Epitope name** KK11

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A02, A11, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** Vif (158–168)

**Author Location** Vif (158–168)

**Epitope** KTKPPLPSVKK

**Epitope name** A3-KK11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 2/7 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Vif (158–168)

**Author Location** Vif (158–168)

**Epitope** RRPPLPSIAK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

- Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** supervised treatment interruptions (STI), escape, superinfection  
**References** Altfeld *et al.* 2002a
- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response to 25 distinct epitopes, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
  - The second infecting strain had the variant rTkppplsVTK. The patient maintained persistent reactive CTL against both variants after the superinfection was established.

- HXB2 Location** Vif (158–168)  
**Author Location** Vif  
**Epitope** RIKPPLPSVTK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A1, A3, B57, B7, Cw6, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a
- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - RIKPPLPSVTK had to mutations overtime, in positions 1 and 10: KikpplpsvKk

- HXB2 Location** Vif (158–168)  
**Author Location** Vif  
**Epitope** KIKPPLPSVTK  
**Epitope name** KK11  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A1, A3, B57, B7, Cw6, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a
- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - One escape mutation, at position 10, KIKPPLPSvKk, was found in the most polymorphic residue in the epitope.

- HXB2 Location** Vif (158–168)  
**Author Location** Vif  
**Epitope** KTKPPLPSVKK

- Epitope name** A3-KK11(Vif)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
  - The most frequently recognized epitopes also elicited the greatest CTL response.
  - HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
  - HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
  - In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

- HXB2 Location** Vif (160–169)  
**Author Location** Vif  
**Epitope** KPPLPSVKKL  
**Immunogen**  
**Species (MHC)** human (B7)  
**References** De Groot *et al.* 2001
- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
  - A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFN $\gamma$  production in an ELISPOT assay.
  - KPPLPSVKKL was newly identified as an HLA-B7 epitope in this study.

- HXB2 Location** Vif (160–169)  
**Author Location** Vif  
**Epitope** KPPLPSVKKL  
**Epitope name** 1296  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Donor MHC** A03, A24, B07, B38, Cw07, Cw12/13  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, computational epitope prediction  
**References** De Groot *et al.* 2003
- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
  - Estimated binding probability for KPPLPSVKKL: 23%

**HXB2 Location** Vif (168–176)  
**Author Location** Vif  
**Epitope** KLTEDRWNK  
**Epitope name** 1344  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A03, A24, B27, B57, Cw13, Cw18  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, computational epitope prediction  
**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KLTEDRWNK: 54%

**HXB2 Location** Vif  
**Author Location** Vif  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Nef, Vif, Vpu  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Keywords** subtype comparisons, Th1  
**References** Ayyavoo *et al.* 2000

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-gamma levels.
- Antigen stimulation increased IFN-gamma production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization-stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

**HXB2 Location** Vif  
**Author Location** Vif  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Nef, Vif, Vpu  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Keywords** subtype comparisons, Th1  
**References** Ayyavoo *et al.* 2000

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-gamma levels.
- Antigen stimulation increased IFN-gamma production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.

- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization-stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

**HXB2 Location** Vif  
**Author Location** Vif  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12  
**Species (MHC)** mouse  
**References** Kim *et al.* 1997c

- A gag/pol, vif or env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice.
- When IL-12 was present, CTL response could be detected even without *in vitro* stimulation.

## II-B-17 Vpr CTL/CD8+ epitopes

**HXB2 Location** Vpr (1–18)  
**Author Location** Vpr  
**Epitope** MEQAPENQGLQREPYNEW  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A28, A29, B14, B44, Cw8  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope. A mutation occurred over time in an individual that reacted to this peptide: MEQAPENQG-pQREPYNEW.

**HXB2 Location** Vpr (7–15)  
**Author Location** Vpr (7–15)  
**Epitope** DQGPQREPY  
**Subtype** B  
**Immunogen** HIV-1 infection, peptide-HLA interaction  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** immunodominance  
**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, DQGPQREPY, is similar to human protein Carcinoma associated protein, sequence qRP-DQGPQRPP, and human proline-rich protein, sequence DQG-PQRpP.

**HXB2 Location** Vpr (9–26)

**Author Location** (C consensus)

**Epitope** GPQREPYNEWTLLELLEEL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0704)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Vpr (9–26)

**Author Location** Vpr

**Epitope** GPQREPYNEWTLLELLEEL

**Epitope name** VPR-02

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.

- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, GPQREPYNEWTLLELLEEL differs from the consensus C sequence GPQREPYNEWTLLELLEEL at 0 amino acid positions, i.e. the two clades' peptides are identical.

**HXB2 Location** Vpr (12–20)

**Author Location** Vpr (12–20 SF2)

**Epitope** REPHNEWTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4002)

**Keywords** acute/early infection

**References** Altfield *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Only one B\*4002+ individual was tested, and had a CTL response against REPHNEWTL.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.

**HXB2 Location** Vpr (12–20)

**Author Location** Vpr (12–20)

**Epitope** REPHNEWTL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4002)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vpr (12–20)

**Author Location** Vpr

**Epitope** REPHNEWTL

**Epitope name** B40-RL9(Vpr)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B40)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Vpr (12–20)

**Author Location**

**Epitope** REPHNEWTL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Vpr (19–28)

**Author Location** Vpr

**Epitope** TLEILEELKN

**Epitope name** TN10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3?)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One mutation, at position 1, Aleileelkn, occurred over time. This is a novel unmapped epitope.

**HXB2 Location** Vpr (25–40)

**Author Location** Vpr (25–40 HXB2)

**Epitope** ELKNEAVRHFPRIWLH

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 17% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** Vpr (25–42)

**Author Location** Vpr

**Epitope** ELKNEAVRHFPRIWLHSL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but



the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.

- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. *J.Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, ELKNEAVRHFPRIWLHSL, had an overall frequency of recognition of 25.3% - 32.2% AA, 19.2% C, 20.5% H, 23.8% WI. This peptide is included in a 27 aa Vpr highly reactive region to be used for vaccine design.

**HXB2 Location** Vpr (29–37)

**Author Location** Vpr (29–37 2001 HIV-1 subtype B cons)

**Epitope** EAVRHFPRI

**Epitope name** EI9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5101)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- Last position (9) in the epitope had potentially experienced positive selection. EAVRHFPRI and EAVRHFPRI escape variants were found.

**HXB2 Location** Vpr (29–37)

**Author Location** Vpr (29–37)

**Epitope** EAVRHFPRI

**Immunogen**

**Species (MHC)** human (B51)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Vpr (29–37)

**Author Location** Vpr (29–37 B)

**Epitope** EAVRHFPRI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A\*0201, A\*2501, B18, B51, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN- $\gamma$  secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** Vpr (29–37)

**Author Location** Vpr

**Epitope** EAVRHFPRI

**Epitope name** EL9

**Immunogen**

**Species (MHC)** (B51)

**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion

**References** Lichtenfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** Vpr (29–37)

**Author Location** Vpr

**Epitope** EAVRHFPRI

**Epitope name** B51-EI9(Vpr)

**Immunogen**

**Species (MHC)** human (B51)

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Vpr (29–43)

**Author Location**

**Epitope** EAVRHFPRILWHLGLG

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN  
*HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A\*2501, A\*3002; B\*0702, B\*1801

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Vpr (29–43)

**Author Location**

**Epitope** EAVRHFPRILWHLGLG

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade MN *HIV component:* gp160

**Species (MHC)** human

**Donor MHC** A1, A33; B44, B8

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.

- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Vpr (30–38)

**Author Location**

**Epitope** AVRHFPRIW

**Epitope name** AW9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B\*57-restricted optimal epitope AVRHFPRIW was tested for immune response.

**HXB2 Location** Vpr (30–38)

**Author Location** Vpr (30–38)

**Epitope** AVRHFPRIW

**Epitope name** vprAV9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Country** United Kingdom, Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** TCR usage, structure, characterizing CD8+ T cells

**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.
- In addition, immunodominance of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFNPEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** Vpr (30–38)

**Author Location** Vpr (29–38 SF2)

**Epitope** AVRHFPRIW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** acute/early infection

**References** Altfield *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.

- This epitope was recognized by 4/6 individuals expressing B\*5701 allele.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.

**HXB2 Location** Vpr (30–38)

**Author Location** Vpr (29–38)

**Epitope** AVRHFPRW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vpr (30–38)

**Author Location** Vpr (30–38)

**Epitope** AVRHFPRW

**Immunogen**

**Species (MHC)** human (B\*5701)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Vpr (30–38)

**Author Location**

**Epitope** AVRHFPRW

**Epitope name** Vpr-AW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 1/7 (14%) recognized this epitope.

**HXB2 Location** Vpr (30–38)

**Author Location** Vpr (30–38)

**Epitope** AVRHFPRW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Vpr (30–38)

**Author Location**

**Epitope** AVRHFPRW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

**HXB2 Location** Vpr (30–38)

**Author Location** Vpr

**Epitope** AVRHFPRW

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B63)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 30% of B63-positive subjects and 14% of B57/58-positive subjects.

**HXB2 Location** Vpr (30–38)

**Author Location**

**Epitope** AVRHFPRW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Vpr (31–39)**Author Location** Vpr (31–39)**Epitope** VRHFPRIWL**Immunogen** HIV-1 infection**Species (MHC)** human (B27)**Keywords** optimal epitope**References** Frahm *et al.* 2008**HXB2 Location** Vpr (31–50)**Author Location** Vpr (31–50)**Epitope** VRHFRPWLHSLGQYIYETY**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanaans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Vpr (34–42)**Author Location** Vpr (34–)**Epitope** FPRPWLHGL**Epitope name** Vpr34**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* Vpr  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** binding affinity, subtype comparisons, computational epitope prediction**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced a CD8+ T-cell IFN gamma response in 1/6 mice. Responses were detected in 3/17 HIV+ HLA-A2 subjects.

**HXB2 Location** Vpr (34–42)**Author Location** Vpr (34–42 SF2)**Epitope** FPRIWLHGL**Epitope name** FL9**Immunogen** HIV-1 infection**Species (MHC)** human (B\*0702)**Keywords** acute/early infection**References** Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- This epitope was recognized by 2/2 individuals expressing B\*8101 allele and 4/8 individuals expressing B\*0702 allele.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.
- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- FPRIWLHGL was the only epitope identified in Vpr for AC-06.

**HXB2 Location** Vpr (34–42)**Author Location** Vpr (34–42)**Epitope** FPRIWLHGL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*0702)**Keywords** early-expressed proteins**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vpr (34–42)  
**Author Location** Vpr (34–42)  
**Epitope** FPRIWLHGL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Vpr (34–42)  
**Author Location** Vpr  
**Epitope** FPRIWLHGL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702)  
**Donor MHC** A\*0301, A\*2301, B\*0702, B\*1503  
**Country** United States  
**Keywords** escape, acute/early infection  
**References** Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- H to Y mutation was observed in position 7.

**HXB2 Location** Vpr (34–42)  
**Author Location** (C consensus)  
**Epitope** FPRWLHGL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FPRWLHGL is an optimal epitope for B\*4201, B\*8101, and B\*0702.

**HXB2 Location** Vpr (34–42)  
**Author Location** Vpr (34–42)  
**Epitope** FPRPWLHSL  
**Epitope name** FL9  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702, B\*4201, B\*8101)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other  
**Keywords** supertype, cross-presentation by different HLA, TCR usage  
**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction
- Only B\*0702 was associated with variation within this epitope.

**HXB2 Location** Vpr (34–42)  
**Author Location** (C consensus)  
**Epitope** FPRWLHGL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FPRWLHGL is an optimal epitope for B\*4201, B\*8101, and B\*0702.

**HXB2 Location** Vpr (34–42)  
**Author Location** Vpr (34–42 SF2)  
**Epitope** FPRIWLHGL  
**Epitope name** FL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*8101)  
**Keywords** acute/early infection  
**References** Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- This epitope was recognized by 2/2 individuals expressing B\*8101 allele and 4/8 individuals expressing B\*0702 allele.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.

**HXB2 Location** Vpr (34–42)  
**Author Location** Vpr (34–42)  
**Epitope** FPRIWLHGL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*8101)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vpr (34–42)

**Author Location** Vpr (34–42)

**Epitope** FPRIWLHGL

**Immunogen**

**Species (MHC)** human (B\*8101)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Vpr (34–42)

**Author Location** (C consensus)

**Epitope** FPRWLHGL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FPRWLHGL is an optimal epitope for B\*4201, B\*8101, and B\*0702.

**HXB2 Location** Vpr (34–42)

**Author Location** (C consensus)

**Epitope** FPRPWLHGL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702, B\*4201, B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Vpr (34–42)

**Author Location**

**Epitope** FPRIWLHGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B07, B81)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA associations (B07, B81), an additional HLA (B42) was statistically predicted to be associated with this epitope.

**HXB2 Location** Vpr (34–42)

**Author Location** Vpr (34–42)

**Epitope** FPRIWLHGL

**Epitope name** B7-FL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 1/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Vpr (34–42)

**Author Location** Vpr (34–42)

**Epitope** FPRTWLHGL

**Epitope name** B7-FL9 Vpr

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection

**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.
- The second infecting strain had the variant fpWtlhgl. The CTL response declined over time and the response to the second variant was lower than to the first one all the time points.

**HXB2 Location** Vpr (34–42)

**Author Location** Vpr

**Epitope** FPRIWLHGL

**Epitope name** FL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A2, B44, B7, Cw5, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 8, FPRIWLHdL was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** Vpr (34–42)

**Author Location** Vpr (34–42)

**Epitope** FPRIWLHGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Vpr (34–42)

**Author Location** Vpr

**Epitope** FPRIWLHGL

**Epitope name** B7-FL9(Vpr)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Vpr (34–42)

**Author Location**

**Epitope** FPRIWLHGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Vpr (41–49)

**Author Location** Vpr

**Epitope** SLGQHIYET

**Epitope name** Vpr41

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* anchored gp120, Vpr *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)

**Assay type** T-cell Elispot, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

**HXB2 Location** Vpr (41–55)

**Author Location**

**Epitope** GLGQHIYETYGDTWA

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A3, A32; B38, B64

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was recognized by a placebo patient after infection.

**HXB2 Location** Vpr (41–57)

**Author Location** (C consensus)

**Epitope** GLGQYIYETYGDTWTGV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*66)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Vpr (46–54)

**Author Location** Vpr (46–54 2001 HIV-1 subtype B cons)

**Epitope** IYETYGDTW

**Epitope name** IW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2501)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

**HXB2 Location** Vpr (48–57)

**Author Location** (C consensus)

**Epitope** ETYGDTWTGV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6802)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the W7 residue of ETYGDTWTGV are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** Vpr (48–57)

**Author Location** Vpr (48–57)

**Epitope** ETYGDTWTGV

**Immunogen**

**Species (MHC)** human (A\*6802)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an A\*6802 epitope.

**HXB2 Location** Vpr (48–57)

**Author Location** Vpr (48–57)

**Epitope** ETYGDTWTGV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6802)

**Assay type** Other

**Keywords** HLA associated polymorphism

**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid



with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.

- ETYGDWTGV was a previously defined A\*6802 presented epitope that encompassed a supertype A\*2 associated polymorphism, YleTYGDWTGV, in the first position of that epitope.
- The epitope YleTYGDWTGV is partially embedded in a CTL immunodominant region.

**HXB2 Location** Vpr (52–62)  
**Author Location** Vpr (52–62)  
**Epitope** DTWAGVEAIIR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*6801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Vpr (53–63)  
**Author Location** Vpr (53–63)  
**Epitope** TWAVEAIIRI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A1, A3, B14, B7, Cw\*0702, Cw\*0802  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** acute/early infection, early-expressed proteins  
**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15–92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** Vpr (55–70)  
**Author Location** Vpr  
**Epitope** AGVEAIIRILQLLFI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** early-expressed proteins  
**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot – 40% (28/70) targeted one or more Vpr peptides, and this peptide was the most frequently recognized epitope in Vpr (41%).
- The regulatory proteins Rev and Tat combined contributed to 3%, and the accessory proteins Vif, Vpr and Vpu to 7%, of the total magnitude of HIV-1 specific CTL responses in a subset of 22 HIV-1 infected individuals in whom all HIV-1 proteins were studied.

**HXB2 Location** Vpr (59–67)  
**Author Location** Vpr (59–67)  
**Epitope** AIIRILQQL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, AIIRILQQL, was detected within overlapping peptides ETYGDWTWAGVEAIIRIL and AGVEAIIRILQQL-FIHF.

**HXB2 Location** Vpr (59–67)  
**Author Location** Vpr (58–66 LAI)  
**Epitope** AIIRILQQL  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (A\*0201)  
**Keywords** optimal epitope  
**References** Altfeld *et al.* 2001c; Frahm *et al.* 2008

- C. Brander notes this is an A\*0201 epitope.

**HXB2 Location** Vpr (59–67)  
**Author Location** Vpr (58–66 SF2)  
**Epitope** AIIRILQQL  
**Epitope name** AL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** acute/early infection  
**References** Altfeld *et al.* 2001a

- CTL responses against HIV-1 Vpr, Vpu, and Vif were analyzed in multiple HIV-1-infected individuals.
- This epitope was recognized by 8/24 individuals expressing A\*0201 allele.

- Epitope is located within a highly conserved alpha helix in Vpr.
- Individuals with long-term nonprogressive and treated chronic HIV-1 infection targeted Vpr more frequently than individuals with treated acute infection.
- Vpr is a frequent target of HIV-1 specific CD8+ T-cells – a response was detected in 45% of individuals tested and Vpr and p17 were the most preferentially targeted proteins per unit length by CD8+ T-cells.
- The A2 epitopes Vpr AIIRLLQQL and p17 SLYNTVATL do not account for the dominance of Vpr and p17, the result holds even when HLA-A2+ individuals are excluded.

**HXB2 Location** Vpr (59–67)

**Author Location** Vpr (59–)

**Epitope** AIIRILQQL

**Epitope name** Vpr-59

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity, subtype comparisons, super-type, computational epitope prediction, immunodominance

**References** Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- AIIRILQQL binds to four HLA-A2 supertype alleles: A\*0203, A\*0201, A\*0206 and A\*6802 (highest affinity), but not A\*0202.
- 5/22 individuals with chronic HIV-1 infection recognized this epitope, but with low magnitude responses in ELISPOT.
- 2/12 HLA-A2 patients with acute HIV-1 infection responded strongly to this peptide, but during chronic infection SL9 and Gag-386 tended to be immunodominant while Vpr-59 was weak and sub-dominant.
- One of the the acutely infected individuals, AC13, was HLA A\*0201/68 B44/14 and also had a strong acute response to gp41 epitope SV10 LLNATDIAV.
- This peptide was shown to be properly processed and presented in TAP-competent B-cell lines *in vitro*.

**HXB2 Location** Vpr (59–67)

**Author Location** Vpr (58–66)

**Epitope** AIIRILQQL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.

- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vpr (59–67)

**Author Location** Vpr (59–67)

**Epitope** AIIRILQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Donor MHC** A\*0201, A32, B49, B51, Cw1, Cw7

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** Vpr (59–67)

**Author Location** Vpr (53–63)

**Epitope** TWAGVEAIIRI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less

frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.

- This epitope, TWAGVEAIIRI, was detected within overlapping peptides ETYGDTWAGVEAIIRIL and AGVEAIIR-ILQLFIHF.

**HXB2 Location** Vpr (59–67)

**Author Location** Vpr

**Epitope** AIIRILQQL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A\*0201 restricted epitope, AIIRILQQL, was mutated to AI(L)RILQQL in the daughter D2 isolate.

**HXB2 Location** Vpr (59–67)

**Author Location** Vpr (59–)

**Epitope** AIIRILQQL

**Epitope name** AL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** acute/early infection

**References** Goulder *et al.* 2001a

- Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia.
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation.

**HXB2 Location** Vpr (59–67)

**Author Location** Vpr (59–67 SF2)

**Epitope** AIIRILQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 0/6 group 2, and 0/4 group 3.

**HXB2 Location** Vpr (59–67)

**Author Location**

**Epitope** AIIRILQQL

**Epitope name** Vpr-AL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 4/35 (11%) recognized this epitope.

**HXB2 Location** Vpr (59–67)

**Author Location** Vpr (59–67)

**Epitope** ALIRILQQL

**Epitope name** AL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** escape, optimal epitope

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For one of the escape variants, a novel CD8 T-cell response equal in magnitude to the wild type, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wild type.
- An escape mutation occurred at position 5 of this epitope, alirSlqql.

**HXB2 Location** Vpr (59–67)

**Author Location** Vpr

**Epitope** ALIRILQQL

**Epitope name** AL9

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Donor MHC** A11, A2, B18, B44, Cw12, Cw5**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 5, ALIRsLQQL, was found in the most polymorphic residue in the epitope. One escape mutation, at position 3, ALtRILQQL was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** Vpr (59–67)**Author Location** Vpr (59–67)**Epitope** ALIRILQQL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding**Keywords** escape, acute/early infection, variant cross-recognition or cross-neutralization, optimal epitope**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was recognized both in acute and chronic infection, but slightly more frequently in chronic infection.
- A less common form of this epitope, with the I to L change in the second position, ALIRILQQL binds to HLA-A2 at lower concentrations and can serve as an HLA-A2 epitope during acute infection. It binds well to A\*0201, A\*0202, A\*0203, and A\*0206. This is an example of a less immunogenic form of the epitope, AiRILQQL becoming the most common circulating form.

**HXB2 Location** Vpr (59–67)**Author Location** Vpr**Epitope** AIIRILQQL**Epitope name** A2-AL9(Vpr)**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.

- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Vpr (59–67)**Author Location** Vpr (59–67)**Epitope** AIIRILQQL**Immunogen** HIV-1 infection**Species (MHC)** human (A2 supertype)**Keywords** supertype, rate of progression**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind four of the five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

**HXB2 Location** Vpr (59–67)**Author Location****Epitope** AIIRILQQL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** epitope processing, escape**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.

- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

- HXB2 Location** Vpr (62–70)  
**Author Location** Vpr (62–)  
**Epitope** RILQQLLFI  
**Epitope name** Vpr-62  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** binding affinity, subtype comparisons, super-type, computational epitope prediction  
**References** Altfeld *et al.* 2001c
- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
  - Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
  - This epitope binds to three HLA-A2 supertype alleles: A\*0202, A\*6802 (strongest affinity) and A\*0203.
  - 3/22 chronically infected patients had a weak ELISPOT response to this epitope.
  - 0/12 HLA-A2 patients with acute HIV-1 infection responded to this peptide.

- HXB2 Location** Vpr (62–70)  
**Author Location** Vpr (62–70)  
**Epitope** RILQQLLFI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** early-expressed proteins  
**References** Addo *et al.* 2002b
- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
  - 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
  - All known optimally defined epitopes were summarized for the five proteins.

- HXB2 Location** Vpr (62–70)  
**Author Location** Vpr  
**Epitope** RILQQLLFI  
**Epitope name** Vpr 62  
**Subtype** M  
**Immunogen** vaccine, in vitro stimulation or selection  
**Vector/Type:** DNA, peptide **Adjuvant:** Incomplete Freund's Adjuvant (IFA)  
**Species (MHC)** human, mouse, humanized mouse (A\*0201)

- Assay type** Cytokine production, T-cell Elispot  
**Keywords** subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization

**References** McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A\*0201 and A\*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- A total of 23 variant forms of Vpr 62 were identified. More than 95% of the variant epitopes were recognized by CTLs from mice immunized with the parental form.
- Vpr 62 epitope (parent or variant form) was present in 96% of HIV sequences of many M group subtypes.

- HXB2 Location** Vpr (62–70)  
**Author Location** Vpr (62–70)  
**Epitope** RILQQLLFI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding  
**Keywords** acute/early infection, optimal epitope  
**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection.

- HXB2 Location** Vpr (62–70)  
**Author Location** Vpr  
**Epitope** RILQQLLFI  
**Epitope name** A2-RI9(Vpr)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Vpr (62–70)**Author Location** Vpr (62–70)**Epitope** RILQQLLFI**Immunogen** HIV-1 infection**Species (MHC)** human (A2 supertype)**Keywords** supertype, rate of progression**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind three of the five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

**HXB2 Location** Vpr**Author Location****Epitope****Immunogen** vaccine*Vector/Type:* adenovirus *HIV component:*

Gag-Pol, Nef, Vpr

**Species (MHC)** mouse**References** Muthumani *et al.* 2002

- Vpr can cause cells to go into G2 arrest, and it suppresses immune cell activation and inflammatory cytokine production, so co-immunization of BALB/c mice with recombinant adenovirus expressing Vpr and HIV-1 antigens Nef or Gag/Pol was tested to see if Vpr reduced the immune response to the other HIV antigens.
- Vpr compromised CD8+ T-cell lytic responses and T-helper proliferative responses in mice co-immunized with Vpr and Nef or Gag/Pol.
- In vitro, Vpr reduced T-cell cytokine production of IL-12 and TNFalpha, indicative of Vpr-mediated immune suppression.

## II-B-18 Tat CTL/CD8+ epitopes

**HXB2 Location** Tat (2–11)**Author Location** (LAI)**Epitope** EPVDPRLPEPW**Subtype** B**Immunogen****Species (MHC)** (B\*5301)**Keywords** optimal epitope**References** Addo *et al.* 2001; Frahm *et al.* 2008**HXB2 Location** Tat (2–11)**Author Location****Epitope** EPVDPRLPEPW**Epitope name** Tat-EW10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5301)**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B\*5301, 3/15 (20%) recognized this epitope.

**HXB2 Location** Tat (2–11)**Author Location** (C consensus)**Epitope** EPVDPNLEPW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5301)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** characterizing CD8+ T cells**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Tat (2–11)**Author Location** (C consensus)**Epitope** EPVDPNLEPW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5301)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- EPVDPNLEPW is an optimal epitope.

**HXB2 Location** Tat (2–11)**Author Location** Tat (2–11 BRU)**Epitope** EPVDPRLPEPW**Epitope name** Tat 1**Immunogen** HIV-1 infection**Species (MHC)** human (B53)**References** Addo *et al.* 2001

- Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides.
- 11/57 (19.3%) HIV-1 + individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide.

- EPVDPRLEPW was recognized by four individuals, but only two were B53, thus this epitope can probably be presented by other HLA alleles.

**HXB2 Location** Tat (2–11)

**Author Location** Tat (2–11)

**Epitope** EPVDPRLEPW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Tat (2–11)

**Author Location** Tat

**Epitope** EPVDPRLEPW

**Epitope name** EW10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** class I down-regulation by Nef

**References** Bobbitt *et al.* 2003

- Nef, through Nef-mediated MHC-1 down-regulation, is not the only viral protein to influence levels of HIV-specific CTL recognition. The Rev L60F mutation, a common natural variant, can decrease CTL recognition of late gene products. The Rev mutation impacts the early to late gene switch, reducing late gene product production (Gag, Pol, Env, Vpu, Vpr and Vif), while increasing Nef production, both of which reduce the impact CTL recognition of late gene products. As expected, Rev L60F rendered HIV infected cells more resistant to CTL that recognized epitopes from the late proteins Env and Gag. Gag expression is reduced more than Env, and Gag-specific CTL were more profoundly affected. Conversely CTL against an epitope in an early gene product, Tat, were more efficiently recognized when infected with viruses carrying the Rev L60F mutation.
- Patients in the asymptomatic phase with active immune responses had more CTL resistant viruses, with lower Rev activity, lower Gag expression and greater resistance to Gag-specific CTL killing, while viruses isolated from people with AIDS were more sensitive to CTL killing.

**HXB2 Location** Tat (2–11)

**Author Location**

**Epitope** EPVDPRLEPW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.

- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope EPVDPRLEPW elicited a magnitude of response of 405 SFC with a functional avidity of 0.075nM and binding affinity of 54.

**HXB2 Location** Tat (2–11)

**Author Location**

**Epitope** EPVDPRLEPW

**Immunogen**

**Species (MHC)** human (B58)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B58 epitope.

**HXB2 Location** Tat (2–11)

**Author Location**

**Epitope** WPVDPRLEPW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Tat (3–11)

**Author Location** Tat (3–11 HXB2)

**Epitope** PVDPRLEPW

**Epitope name** PW9

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (A\*2501)**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape, immune evasion, optimal epitope**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Positions 5 and 7 in the epitope had potentially experienced positive selection. PVD-PRLdPW, PVDPsLEPW and PVDPkLEPW escape variants were found.

**HXB2 Location** Tat (12–21)**Author Location** Tat (12–21 SUMA)**Epitope** KHPGSQPKTA**Epitope name** Tat KA10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** Tat (16–30)**Author Location** Tat (16–30)**Epitope** SQPKTACNKCYCKRC**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Tat (17–25)**Author Location****Epitope** QPKTACTNC**Immunogen** vaccine*Vector/Type:* DNA *HIV component:* Tat  
*Adjuvant:* E. coli heat labile enterotoxin**Species (MHC)** mouse (H-2d)**Assay type** Chromium-release assay**Keywords** vaccine antigen design**References** Morris *et al.* 2001a

- To identify a peptide capable of inducing a Tat-specific CTL response, overlapping 9mers were used to immunize mice intranasally. This Tat epitope maps within a region previously identified as the site of T- and B-cell epitopes identified in HIV patients.

**HXB2 Location** Tat (17–25)**Author Location****Epitope** QPKTACTNC**Immunogen** vaccine*Vector/Type:* ISCOM *Strain:* multiple epitope immunogen *HIV component:* Env, Gag, Tat**Species (MHC)** mouse (H-2d)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** vaccine antigen design**References** Pahar *et al.* 2006

- Rhesus macaques were immunized intrarectally with an ISCOM vaccine containing a single SIV-Gag CTL epitope, a single human HIV-Env Th epitope, plus a negative control mouse H-2d Tat epitope. Following challenge with SHIV-SF162p4, immunized macaques became infected, but had significantly lower viral loads than non-immunized animals.
- This epitope was used as a negative control; it is a known mouse epitope, but is non-reactive in primates.

**HXB2 Location** Tat (17–26)**Author Location** Tat (17–26)**Epitope** QPKTACTTCY**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Keywords** early-expressed proteins**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.



- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Tat (17–26)

**Author Location**

**Epitope** QPKTACTTCY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Tat (18–26)

**Author Location** Tat (18–26)

**Epitope** PKTACTNCY

**Subtype** B

**Immunogen** HIV-1 infection, peptide-HLA interaction

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** immunodominance

**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host

proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.

- This HIV-1 epitope, PKTACTNCY, is similar to human protein Zinc finger protein, sequence SQPKsACgNCY.

**HXB2 Location** Tat (20–28)

**Author Location** Tat

**Epitope** TACNNCYCK

**Epitope name** 1342

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, A23, B49, B57

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for TACNNCYCK: 46%

**HXB2 Location** Tat (20–29)

**Author Location** Tat

**Epitope** TACNNCYCKK

**Epitope name** 1279

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A68)

**Donor MHC** A01, A68, B15, B40, Cw03

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for TACNNCYCKK: 74%. This peptide bound A68, not A11.

**HXB2 Location** Tat (24–32)

**Author Location** Tat (24–32 BORI)

**Epitope** NCYCKKCCY

**Epitope name** Tat NY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2902)

**Donor MHC** A\*2902, B\*1402, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- There were five variants of the NCYCKKCCY epitope in BORI, and new changes kept accruing. kCYCKKCCY was apparent by day 31, kCYCKrCCY by day 218, and kCYCK-qCCY by day 556; all conferred escape, the double mutants abrogating the response. NCYCKKyCY and NCYCKKCCc were also transiently present at day 55, but were not tested for CTL escape.

**HXB2 Location** Tat (24–32)

**Author Location** Tat (24–32 WEAU)

**Epitope** NCYCKRCCF

**Epitope name** Tat NF9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2902)

**Donor MHC** A\*2902, B\*0801, B\*4403

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.

- There was a weak response to this epitope during acute infection that was lost by early infection. The epitope variant kCYCKRCCF was evident by day 72, and other variants were evident in samples taken at 391 and 772 days, including NCYCKkCCF, tCYCKRCCF, kCYCKsCCF and kCYCKkCCF. It was not determined if these were specifically escape mutations, but the CTL response diminished in vivo as kCYCKRCCF variant came up.

**HXB2 Location** Tat (24–32)

**Author Location** Tat (24–32)

**Epitope** NCYCKKCCF

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*2902, B\*1402; A\*2902, B\*0801, B\*4403

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rates for this epitope, NCYCK-KCCF, were found to be 0.047 and 0.006/day (optimistic escape rates = 0.051 and 0.013), with SE of 0.054 and 0.004 respectively.
- In the first subject, 3 mutations in this Tat epitope (N24K, N24K+K29R, N24K+K29Q) were all shown to confer escape. In the second subject, peptide recognition was not tested, but by analogy with another patient it was suggested that a N to K mutation at position 1 of the epitope Tat 24-32 conferred escape. An additional N to T mutation at position 1 was also considered likely to be an escape mutation.

**HXB2 Location** Tat (29–43)

**Author Location** Tat (29–43)

**Epitope** KCCFHCQVCFTTKGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*03, A\*24, B\*35, B\*40

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, variant cross-recognition or cross-neutralization, superinfection, characterizing CD8+ T cells

**References** Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- A early response to this peptide KCCFHCQVCFTTKGL was detected that waned prior to superinfection. The embedded epitope and HLA presenting molecule were not resolved. The initial and superinfecting strains had different versions of the peptide, oCCFHCQVCFTTKGL and KCCIHCQVCFTTKGL respectively.

**HXB2 Location** Tat (30–37)**Author Location** Tat (30–37)**Epitope** CCFHCQVC**Immunogen****Species (MHC)** human (Cw\*12)**Keywords** optimal epitope**References** Frahm *et al.* 2008**HXB2 Location** Tat (30–37)**Author Location** Tat (30–37)**Epitope** CCFHCQVC**Epitope name** CC8**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*12)**Donor MHC** A11, A2, B18, B44, Cw12, Cw5**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay**Keywords** escape, optimal epitope**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- A mutation occurred at position 3 of this epitope, ccMhcqvc, but significant cross-recognition was observed between the escape variant and the wildtype epitope.

**HXB2 Location** Tat (30–37)**Author Location** Tat**Epitope** CCFHCQVC**Epitope name** CC8**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*12)**Donor MHC** A11, A2, B18, B44, Cw12, Cw5**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 3, CCIHCQVC, was found in the most polymorphic residue in the epitope.

**HXB2 Location** Tat (30–37)**Author Location** Tat**Epitope** CCFHCQVC**Epitope name** CC8**Immunogen****Species (MHC)** (Cw\*12)**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion**References** Lichtenfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** Tat (30–37)**Author Location** Tat (30–37)**Epitope** CCFHCQVC**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*1203)**Donor MHC** A26, A3, B\*3801, B7, Cw\*0702, Cw\*1203; A\*0201, A\*2501, B18, B51, Cw\*0102, Cw\*1203**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** acute/early infection, early treatment**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN- $\gamma$  secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- Two individuals recognized this epitope both presented by Cw\*1203.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

**HXB2 Location** Tat (30–37)

**Author Location** Tat (30–37)

**Epitope** CCFHCQVC

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*1203)

**Donor MHC** A26, A3, B\*3801, B7, Cw\*0702, Cw\*1203; A\*0201, A\*2501, B18, B51, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, early treatment

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15–92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- Two individuals recognized this epitope both presented by Cw\*1203.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

**HXB2 Location** Tat (30–37)

**Author Location** Tat (30–37 HXB2)

**Epitope** CCFHCQVC

**Epitope name** CC8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*1203)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at

high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

- Position 3 in the epitope had potentially experienced positive selection. CCIHCQVC and CCFHCQsC escape variants were found.

**HXB2 Location** Tat (30–37)

**Author Location**

**Epitope** CCFHCQVC

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120

*boost Strain:* B clade LAI, B clade MN

*HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A\*2501, A\*3002; B\*0702, B\*1801

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85–86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Tat (31–39)

**Author Location** Tat (31–39)

**Epitope** CLHCQVCFI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A2, B13, B41

**Country** France

**Assay type** Other

**Keywords** computational epitope prediction, escape, acute/early infection, immune evasion

**References** Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- The predicted epitope C(I)HCQVCFI, had a variant CfHCQVCFI in the second position.

**HXB2 Location** Tat (32–41)

**Author Location** Tat (32–41 SUMA)

- Epitope** FHCQVCFMTK  
**Epitope name** Tat FK10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** dynamics, epitope processing, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion  
**References** Jones *et al.* 2004
- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
  - The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
  - Only four epitopes were found to acquire escape mutations in SUMA over time. Early in infection, three overlapping epitopes in Tat carried mutations: FHCQVCFMTK, VCFMTKGLGI, and MTKGLGISY. An M->T substitution was evident during acute infection in the first sample, at four days of the onset of symptoms, and a rare second variant was seen at day 20 that added a K->E substitution. The M->T substitution abrogated responses to FHCQVCFrTK, VCFrTKGLGI, but not in the third epitope rTKGLGISY. By day 69 a double mutation was evident that persisted through day 435, F->L and T->K. Variants IHCQVCFmKk, VCFmKkGLGI were not recognized, and impact processing of the MkkKGLGISY epitope.
- HXB2 Location** Tat (32–41)  
**Author Location** Tat (32–41)  
**Epitope** FHCQVCFITK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** HAART, ART, escape, viral fitness and reversion  
**References** Asquith *et al.* 2006
- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is

made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.

- The best estimate of escape rate for this epitope, FHCQVCFITK, was found to be 0.066 (optimistic escape rate = 0.189) per day, with SE of 0.032.
- In this region of Tat there were 3 overlapping CTL epitopes. A T to K mutation at Tat 32 completely abolished in vitro CTL lysis against all three epitopes. In addition, an M to T mutation at Tat 31 completely abolished recognition of two of the epitopes (third not tested). Quantifying the outgrowth of both of the mutations will overestimate the efficiency of a single CTL response.

**HXB2 Location** Tat (32–49)

**Author Location** Tat

**Epitope** FHCQVCFrTKGLGISYGR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were

not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.

- This immunodominant, frequently targeted overlapping peptide, FHCQVCFTTKGLGISYGR, had an overall frequency of recognition of 16.7% - 16.9% AA, 15.4% C, 20.5% H, 9.5% WI.

**HXB2 Location** Tat (36–45)

**Author Location** Tat (36–45)

**Epitope** VCFTTKGLGI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*15)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, VCFTTKGLGI, was detected within overlapping peptides FHCQVCFTTKGLGISYGR and TKGLGISYGRKKRRQRRR.

**HXB2 Location** Tat (36–45)

**Author Location** Tat (36–45 SUMA)

**Epitope** VCFMTKGLGI

**Epitope name** Tat VII0

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1501)

**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, epitope processing, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single

patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.

- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time. Early in infection, three overlapping epitopes in Tat carried mutations: FHCQVCFMTK, VCFMTKGLGI, and MTKGLGISY. An M->T substitution was evident during acute infection in the first sample, at four days of the onset of symptoms, and a rare second variant was seen at day 20 that added a K->E substitution. The M->T substitution abrogated responses to FHCQVCFTK, VCFMTKGLGI, but not in the third epitope tTKGLGISY. By day 69 a double mutation was evident that persisted through day 435, F->L and T->K. Variants IHCQVCFMkK, VCFMkKGLGI were not recognized, and impact processing of the MTKGLGISY epitope.

**HXB2 Location** Tat (36–45)

**Author Location** Tat (36–45)

**Epitope** VCFITKALGI

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, VCFITKALGI, was found to be 0.066 (optimistic escape rate = 0.189) per day, with SE of 0.032.
- In this region of Tat there were 3 overlapping CTL epitopes. A T to K mutation at Tat 32 completely abolished in vitro CTL lysis against all three epitopes. In addition, an M to T mutation at Tat 31 completely abolished recognition of two of the epitopes (third not tested). Quantifying the outgrowth of both of the mutations will overestimate the efficiency of a single CTL response.

**HXB2 Location** Tat (36–50)  
**Author Location** (subtype C)  
**Epitope** VCFQTKGLGISYGRK  
**Subtype** C  
**Immunogen**  
**Species (MHC)** human  
**Keywords** immunodominance, escape  
**References** Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 17 of 46 patients reacted with Tat immunodominant peptide VCFQTKGLGISYGRK.
- Most of the CTL responses occurred despite a mismatch between the autologous viral sequence and peptide – complete matches were seen only in 4 of 19 cases (21%) and the mismatched CTL tended not to respond to the autologous viral peptide indicative of immune escape.

**HXB2 Location** Tat (36–50)  
**Author Location** Tat (36–50)  
**Epitope** VCFQTKGLGISYGRK  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons  
**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Tat (36–52)  
**Author Location** Tat  
**Epitope** VCFTTKALGISYGRKKR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** early-expressed proteins  
**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot – 28% (19/70) targeted one or more Tat peptides, and this peptide was the most frequently recognized epitope in Tat (27%).
- The regulatory proteins Rev and Tat combined contributed to 3%, and the accessory proteins Vif, Vpr and Vpu to 7%, of the total magnitude of HIV-1 specific CTL responses in a subset of 22 HIV-1 infected individuals in whom all HIV-1 proteins were studied.

**HXB2 Location** Tat (38–47)  
**Author Location** (subtype C)  
**Epitope** FQTKGLGISY  
**Epitope name** T38-FY10  
**Subtype** C  
**Immunogen**

**Species (MHC)** human (B\*1503)  
**Keywords** immunodominance  
**References** Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 17 of 46 patients reacted with Tat immunodominant peptide VCFQTKGLGISYGRK.
- FQTKGLGISY was the optimal epitope in the peptide VCFQTKGLGISYGRK among B\*1503+ individuals.

**HXB2 Location** Tat (38–47)  
**Author Location** Tat (38–47)  
**Epitope** FQTKGLGISY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Tat (38–47)  
**Author Location** (C consensus)  
**Epitope** FQTKGLGISY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Tat (38–47)  
**Author Location** (C consensus)  
**Epitope** FQTKGLGISY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FQTKGLGISY is an optimal epitope.

**HXB2 Location** Tat (38–47)

**Author Location** Tat**Epitope** FQTKGLGISY**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*1503)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, rate of progression, immunodominance**References** Frahm *et al.* 2006

- CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects in spite of the same immunodominant responses in subjects infected with either subtype. Clade B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.
- FQTKGLGISY of clade C is a potential HLA-B\*1503 restricted epitope.

**HXB2 Location** Tat (38–47)**Author Location** Tat**Epitope** FQTKGLGISY**Epitope name** B15-FY10(Tat)**Immunogen** HIV-1 infection**Species (MHC)** human (B15)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Tat (39–47)**Author Location** Tat (39–47) SUMA)**Epitope** MTKGLGISY**Epitope name** Tat MY9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*1501)**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** dynamics, epitope processing, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time. Early in infection, three overlapping epitopes in Tat carried mutations: FHCQVCFMTK, VCFMTKGLGI, and MTKGLGISY. An M->T substitution was evident during acute infection in the first sample, at four days of the onset of symptoms, and a rare second variant was seen at day 20 that added a K->E substitution. The M->T substitution abrogated responses to FHCQVCFrTK, VCFrTKGLGI, but not in the third epitope tTKGLGISY. By day 69 a double mutation was evident that persisted through day 435, F->L and T->K. Variants IHCQVCFMkK, VCFMkKGLGI were not recognized, but the CTL response was strong to MkKGLGISY. The authors provide evidence that the F->L and T->K substitutions impact processing of the MTKGLGISY epitope, as the mutations don't abrogate a CTL response to the peptide, but Tat expressed in target cells doesn't allow recognition of the Tat variant.
- MTKGLGISY was the highest level response in acute and early infection.

**HXB2 Location** Tat (39–47)**Author Location** Tat (39–47)**Epitope** ITKALGISY**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** HAART, ART, escape, viral fitness and reversion**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate



for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.

- The best estimate of escape rate for this epitope, VC-FITKALGI, was found to be 0.066 (optimistic escape rate = 0.189) per day, with SE of 0.032.
- In this region of Tat there were 3 overlapping CTL epitopes. A T to K mutation at Tat 32 completely abolished in vitro CTL lysis against all three epitopes. In addition, an M to T mutation at Tat 31 completely abolished recognition of two of the epitopes (third not tested). Quantifying the outgrowth of both of the mutations will overestimate the efficiency of a single CTL response.

**HXB2 Location** Tat (39–49)  
**Author Location** Tat (38–48)  
**Epitope** ITKGLGISYGR  
**Epitope name** Tat-4.8  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*6801)  
**Keywords** assay standardization/improvement  
**References** Oxenius *et al.* 2002a

- This epitope and HLA-A\*6801 presenting molecule were rapidly defined using a modified Elispot assay.
- The 11-mer is the optimal epitope but A\*6801 epitopes tolerate length variation.

**HXB2 Location** Tat (39–49)  
**Author Location** Tat (39–49)  
**Epitope** ITKGLGISYGR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*6801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Tat (39–49)  
**Author Location** Tat (38–48)  
**Epitope** ITKGLGISYGR  
**Epitope name** ITK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*6801)  
**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, escape  
**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and

the relatively efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.

- This was one of 8 reactive epitopes found not to vary over time.

**HXB2 Location** Tat (39–49)  
**Author Location** Tat (38–49)  
**Epitope** ITKGLGISYGR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*6801)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Degranulation, CD107a and b cell surface mobilization, Other  
**Keywords** binding affinity, epitope processing, kinetics, characterizing CD8+ T cells  
**References** Gostick *et al.* 2007

- HLA-A\*6801 was studied because of its unusual property of weak binding to CD8. Several peptide variants were followed in a CTL clone grown from an A\*68 expressing patient who responded to his autologous "index" peptide iTKgLGISYGR. His founder epitope was suggested to be TTKALGISYGR, the "reference" sequence, with variants ITKaLGISYGR and tTKGLGISYGR. The reference sequence TTKALGISYGR is a better agonist in cytokine and degranulation assays than the index peptide iTKgLGISYGR. Surface plasmon resonance shows that both index and reference peptides bind soluble TCR within normal ranges. A mutant HLA-A68 that increases CD8 interaction was found to recognize CTL at lower peptide concentrations and increase cytokine production (IFN-g, MIP-1b, RANTES). However its pattern of variant recognition was not changed. Thus "normalization" of HLA-A\*6801 interaction with CD8 does not induce non-specific activation, but does enhance agonist peptide recognition and immune response.

**HXB2 Location** Tat (39–49)  
**Author Location** Tat (39–49)  
**Epitope** ITKGLGISYGR  
**Subtype** B  
**Immunogen** peptide-HLA interaction  
**Species (MHC)** human (A\*6801)  
**Assay type** Cytokine production, Flow cytometric T-cell cytokine assay  
**Keywords** binding affinity, co-receptor, characterizing CD8+ T cells  
**References** Laugel *et al.* 2007a

- It was found that CD8 co-receptor differentially fine tunes CTL function via cytokine/chemokine production (MCP-1, MIP1-beta, MIP1-alpha, TNF-alpha, RANTES, IFN-gamma, IL-2 and IL-4). Differential CD8 action was controlled by abrogating its engagement using point-mutated HLA Class I molecules in 4 CTL clones specific for 3 different epitopes from HIV-1 and hTERT.
- An HLA-A\*6801 restricted CTL clone, c23, specific for HIV-1 Tat epitope ITKGLGISYGR found to require a much higher peptide concentration to activate effector functions. This clone did not secrete IL-4.

**HXB2 Location** Tat (39–49)  
**Author Location** Tat (38–48)  
**Epitope** ITKGLGISYGR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A68)  
**Keywords** early-expressed proteins  
**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Tat (39–49)  
**Author Location** Tat  
**Epitope** ITKGLGISYGR  
**Epitope name** A68-IR11(Tat)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A68)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Tat (40–47)  
**Author Location** Tat  
**Epitope** TKGLGISY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, rate of progression, immunodominance, characterizing CD8+ T cells  
**References** Frahm *et al.* 2006

- CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects in spite of the same immunodominant responses in subjects infected with either subtype. Clade

B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.

- TKGLGISY of clade B is a potential HLA-B\*1503-restricted epitope, with epitope qTKGLGISY found in clade C.

**HXB2 Location** Tat (40–49)  
**Author Location**  
**Epitope** TKALGISYGR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** epitope processing, escape  
**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Tat (49–57)  
**Author Location** Tat (49–57)  
**Epitope** RKKRRQRRR  
**Immunogen** vaccine  
*Vector/Type:* DNA, DNA with protein boost  
*Strain:* B clade LAI *HIV component:* Gag, Nef, Tat *Adjuvant:* IL-18  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Keywords** Th1  
**References** Billaut-Mulot *et al.* 2001

- DNA vaccinated BALB/c mice primed and boosted with the multi-epitopic vaccine with IL18 showed lymphoproliferative responses 7 weeks post immunization.
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime/DNA boost was more effective than DNA prime protein boost.
- Immunization with either the multi-epitopic DNA or with the mixed DNA vaccine induced HIV-1 specific Th1 cytokines (IL-2 and IFN-gamma)
- Co-administration of IL18 increased T-cell responses but decreased anti-HIV antibody levels.

**HXB2 Location** Tat (49–57)  
**Author Location** Tat (49–57)  
**Epitope** RKKRRQRRR  
**Immunogen**  
**Species (MHC)** mouse  
**References** Kim *et al.* 1997a

- The Tat peptide RKKRRQRRR when conjugated to a protein can cause that protein to be taken up by APCs and presented to CTL.
- The system was demonstrated by vaccinating mice with an OVA-Tat peptide conjugate and immunizing H-2 K<sup>b</sup> mice.
- The CTL response to the H-2 K<sup>b</sup> specific OVA peptide SIIN-FEKL was stimulated.

**HXB2 Location** Tat (58–69)  
**Author Location** Tat  
**Epitope** APQGHNNQVSI  
**Epitope name** AI12  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A2, B44, B7, Cw5, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 4, APQdHPNNQVSI, was found not to correspond to the most polymorphic residue in the epitope. This is a novel unmapped epitope.

**HXB2 Location** Tat (83–92)  
**Author Location** Tat  
**Epitope** GPKESKKKVE  
**Immunogen**  
**Species (MHC)** human (B58)  
**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFN $\gamma$  production in an ELISPOT assay.
- GPKESKKKVE was newly identified as an HLA-B58 epitope in this study.

**HXB2 Location** Tat  
**Author Location** Tat  
**Epitope**  
**Immunogen** vaccine  
**Vector/Type:** adeno-associated virus (AAV)  
**HIV component:** Env, Rev, Tat **Adjuvant:** IL-2

**Species (MHC)** mouse (H-2<sup>d</sup>)  
**References** Xin *et al.* 2001

- An AAV vector expressing HIV-1 env, tat, and rev genes (AAV-HIV vector) was used to vaccinate BALB/c mice.
- A single injection stimulated and long lasting serum IgG, fecal IgA, and HIV-specific CTL.
- Boosting enhanced the humoral response, and IL2 enhanced T-cell immunity.

**HXB2 Location** Tat  
**Author Location** Tat (IIIB)  
**Epitope**  
**Subtype** B  
**Immunogen** vaccine  
**Vector/Type:** protein **Strain:** B clade IIIB  
**HIV component:** Tat **Adjuvant:** Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide (MALP)

**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Assay type** T-cell Elispot  
**References** Borsutzky *et al.* 2003

- BALB/c mice that were vaccinated intranasally with Tat protein plus mucosal adjuvant macrophage-activating lipopeptide-2 (MALP-2) had increased proliferative, antibody, and IFN-gamma producing T-cell responses than did mice with Tat+IFA delivered by the i.p. route.
- IFA as adjuvant stimulated a Th2-dominant response pattern, and MALP-2 as adjuvant shifted to a Th1 response. In animals vaccinated with Tat+MALP-2, IFN-gamma and IL-2 were the most prominent cytokines, with some IL-6. In contrast, in mice vaccinated with Tat+IFA, IL-6 was the dominant cytokine. Secreted IL-4, IL-5 and IL-10 were below the detection limit in both cases.

**HXB2 Location** Tat  
**Author Location** Tat  
**Epitope**  
**Immunogen** vaccine  
**Vector/Type:** protein **HIV component:** Tat  
**Adjuvant:** Complete Freund's Adjuvant (CFA), red blood cells  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Assay type** Chromium-release assay  
**Keywords** dendritic cells, Th1, Th2, immunotherapy  
**References** Dominici *et al.* 2003

- BALB/c mice were immunized with Tat protein bound to red blood cells via biotin-avidin conjugation. This antigen delivery system was successfully internalized by dendritic cells, and induced more consistent anti-Tat Abs responses and slightly increased Tat-specific CTL responses relative to Tat with CFA.

**HXB2 Location** Tat  
**Author Location** Tat  
**Epitope**  
**Immunogen** vaccine  
**Vector/Type:** DNA **HIV component:** Nef, Rev, Tat  
**Species (MHC)** human  
**Keywords** HAART, ART

**References** Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-gamma production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

**HXB2 Location** Tat**Author Location** Tat**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression**References** Froebel *et al.* 1997

- Two HIV-1 infected children with contrasting disease courses were followed longitudinally – one died of AIDS, the other is a long-term non-progressor.
- Reactivity against Gag, Pol, Env and Tat proteins was tested by PBMC bulk cultured cells reacting with protein expressed in vaccinia constructs in autologous EBV transformed B cells.
- The child who progressed consistently had CTL against Pol and Tat.
- The long-term non-progressing child had no detectable CTL, but was heterozygous for a mutation in the CCR5 receptor and for HLA-B49, which has been shown to be associated with slower progression.

**HXB2 Location** Tat**Author Location** Tat**Epitope****Immunogen** HIV-1 infection, vaccine*Vector/Type:* DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)**Species (MHC)** human**Keywords** review**References** Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on the stimulatory role of CpG motifs and how HIV-1 DNA vaccines can boost the CTL and Th proliferative responses in asymptomatic HIV+ individuals.

**HXB2 Location** Tat**Author Location** Tat**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade BH10 *HIV component:* Tat *Adjuvant:* Immune stimulating complexes (ISCOM), CpG immunostimulatory sequence (ISS)**Species (MHC)** macaque**References** Cafaro *et al.* 2001

- Macaques (*macaca fascicularis*) were immunized with HIV-1 Tat on an adenovirus major late promoter in a plasmid with 23 CpG sequences, 12 unmethylated.
- The vaccinated animals contained a primary infection challenge with SHIV89.6P, preventing CD4+ T-cell decline in the animals, suggesting Tat may be useful at blocking viral replication at its early stage.

**HXB2 Location** Tat**Author Location****Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission**References** Aldhous *et al.* 1994; Kuhn *et al.* 2002

- Six of nine HIV vertically infected infants had HIV-1 specific CTL responses to vaccinia expressed Tat (4/6), Pol (6/6), Env (1/6), or Gag (1/6), but not all responses were detected at all time points.
- Two of eleven babies that were not infected though born to HIV+ mothers had detectable responses to Tat (1/2), Pol (2/2), Gag (1/2).
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Tat**Author Location** Tat**Epitope****Immunogen** HIV-1 infection, vaccine**Species (MHC)** human**Keywords** review, escape, early-expressed proteins**References** Gruters *et al.* 2002

- This paper is a review that makes a case for using Tat and Rev as part of a vaccine strategy.
- CTL against Tat and Rev were found preferentially in long term non-progressors.
- Tat/Rev vaccinations of macaques provided protection or reduction in viremia, with high levels of CTL providing protection from challenge, lower levels of CTL having lower viremia, while Gag/Pol vaccinations with did not result in decreased viremia.
- Early expression of Tat/Rev may in part explain the enhanced benefit of a CTL response directed at these proteins, and CTL escape is more prominent in these proteins.

**HXB2 Location** Tat**Author Location** Tat (BH10)**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade BH10 *HIV component:* Tat *Adjuvant:* cationic block copolymer K2**Species (MHC)** mouse**Donor MHC** H-2d**Assay type** proliferation, Chromium-release assay**References** Caputo *et al.* 2003

- Mice were immunized intramuscularly with a plasmid DNA vaccine (HIV-1 pCV-tat DNA) alone or complexed with a cationic block polymer K1, K2, or K5, which block digestion by DNAase I and enhance DNA delivery to APC.
- CTL responses to low dose Tat DNA vaccination with K2 were greatly enhanced relative to responses to DNA alone.

**HXB2 Location** Tat  
**Author Location** Tat  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA, protein *HIV component:* Tat *Adjuvant:* aluminum hydroxide, Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (MHC)** macaque  
**Keywords** review, early-expressed proteins  
**References** Fanales-Belasio *et al.* 2002a

- HIV-1 Tat protein is efficiently taken up by monocyte-derived dendritic cells (MDDCs) and promotes Th1 immune responses. A Tat based vaccine can elicit an immune response that can control primary infection in monkeys that are in early stage of infection with SHIV89.6P.
- Tat-specific CTL activity was detected in four monkeys inoculated with i.m. with pCV-tat.

**HXB2 Location** Tat  
**Author Location** Tat  
**Epitope**  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)**  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** epitope processing, immunodominance, early-expressed proteins, Th1, adjuvant comparison  
**References** Gavioli *et al.* 2004

- HIV-1 Tat protein modulates proteasome composition and activity in B and T cells that either express Tat or are treated with exogenous biologically active Tat protein. This results in modification of Ag processing where presentation of immunodominant EBV epitopes is decreased and presentation of subdominant epitopes is increased. The authors suggest that the immunomodulatory effects of endogenous and exogenous Tat may be beneficial in terms of expanding stimulation of responses to subdominant epitopes, and may be useful as an adjuvant.

**HXB2 Location** Tat  
**Author Location** Tat  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** China  
**Assay type** T-cell Elispot  
**References** Wang *et al.* 2006

- The association between T cell response and CD4+ T cell counts or CD4+ was investigated, using overlapping peptides corresponding to natural B clade and C consensus sequences.

- T cell responses and CD4+ count were correlated for Gag p24 and Gag p17 (B and C clades) and for Pol (C clade). CD4+ counts were higher in patients with Tat and /or Rev T cell response than in patients without Tat and Rev response.

## II-B-19 Rev CTL/CD8+ epitopes

**HXB2 Location** Rev (9–23)  
**Author Location** Rev (9–23 HXB2)  
**Epitope** DEELIRTVRLIKLLY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Blazevic *et al.* 1995

- Induces both Th and CTL activities, no HLA restriction analysis performed.

**HXB2 Location** Rev (9–23)  
**Author Location**  
**Epitope** DEELIRTVRLIKLLY  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41  
**Species (MHC)** human  
**Donor MHC** A1, A10 (26); B17 (57), B8  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes  
**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85–86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Rev (10–18)  
**Author Location** Rev (10–18)  
**Epitope** EELLKTVRL  
**Subtype** B  
**Immunogen** HIV-1 infection, peptide-HLA interaction  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** immunodominance  
**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome

in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.

- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, EELLKTVRL, is similar to human protein nucleolar RNA associated protein, sequence EEL-LKeVRL, and a human protein, sequence LLKTVRLIRLL.

**HXB2 Location** Rev (12–31)

**Author Location** Rev (11–30 SF2)

**Epitope** LLKAVRLIKFLYQSNPPPNF

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Only one subject had CTL that could recognize vaccinia-expressed LAI Rev.
- This subject had a CTL response to this peptide, and was HLA-A2, A24, B13, B35.

**HXB2 Location** Rev (13–21)

**Author Location** Rev (13–21)

**Epitope** LRAVRIIKI

**Epitope name** LI9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701, B\*5703)

**Country** United Kingdom, Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** escape, optimal epitope

**References** Makadzange *et al.* 2006

- The study describes the identification of a novel HLA-B\*5701, B\*5703 optimal epitope LRAVRIIKI, which accounted for 25% and 40% of the total CTL responses in two patients.
- R2K replacement (LkAVRIIKI) resulted in more efficient lysis. I9F (LRAVRIIKf) variant had reduced CTL recognition.

**HXB2 Location** Rev (14–23)

**Author Location**

**Epitope** KAVRLIKFLY

**Epitope name** KY10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses

were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.

- HLA-B\*57-restricted optimal epitope KAVRLIKFLY was tested for immune response.

**HXB2 Location** Rev (14–23)

**Author Location** Rev (14–23)

**Epitope** KAVRLIKFLY

**Epitope name** revKY10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Country** United Kingdom, Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** TCR usage, structure, characterizing CD8+ T cells

**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.
- In addition, immunodominancy of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFN-PEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** Rev (14–23)

**Author Location** Rev (14–23 subtype B)

**Epitope** KAVRLIKFLY

**Subtype** B

**Immunogen**

**Species (MHC)** human (B\*5701)

**Keywords** optimal epitope

**References** Addo *et al.* 2001; Frahm *et al.* 2008

- C. Brander notes this is a B\*5701 epitope.

**HXB2 Location** Rev (14–23)

**Author Location** Rev (14–23 BRU)

**Epitope** KAVRIKFLY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** cross-presentation by different HLA

**References** Addo *et al.* 2001

- Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides.
- 11/57 (19.3%) HIV-1 + individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide.
- This epitope was also recognized by another individual in whom it was restricted by HLA\*B5801, an allele closely related to HLA\*B5701, suggesting cross-presentation by the two HLA alleles.

**HXB2 Location** Rev (14–23)

**Author Location** Rev (14–23)

**Epitope** KAVRRLIKFLY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Rev (14–23)

**Author Location** Rev (14–23 subtype B)

**Epitope** KAVRLIKFLY

**Subtype** B

**Immunogen**

**Species (MHC)** human (B\*5801)

**Keywords** optimal epitope

**References** Addo *et al.* 2001; Frahm *et al.* 2008

- C. Brander notes this is a B\*5801 epitope.

**HXB2 Location** Rev (14–23)

**Author Location** Rev (14–23 BRU)

**Epitope** KAVRIKFLY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801)

**Keywords** cross-presentation by different HLA

**References** Addo *et al.* 2001

- Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides.
- 11/57 (19.3%) HIV-1 + individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide.
- This epitope was also recognized by another individual in whom it was restricted by HLA\*B5701, an allele closely related to HLA\*B5801, suggesting cross-presentation by the two HLA alleles.

**HXB2 Location** Rev (14–23)

**Author Location** Rev (14–23)

**Epitope** KAVRRLIKFLY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Rev (14–23)

**Author Location** Rev

**Epitope** KTGRLIKLLY

**Epitope name** KY10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 8, ktgrlikLly, was found in the most polymorphic residue in the epitope. One escape mutation, at position 5, ktgrFiklly was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** Rev (14–23)

**Author Location**

**Epitope** KAVRLIKFLY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** responses in children, mother-to-infant transmission

**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- This epitope was recognized less frequently in children than in adults.

**HXB2 Location** Rev (14–23)

**Author Location** Rev

**Epitope** KTVRLIKFLY

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B58, B63)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment.

Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.

- This epitope was recognized by 20% of B63-positive subjects and 12% of B57/58-positive subjects.

**HXB2 Location** Rev (14–23)

**Author Location**

**Epitope** KAVRLIKFLY

**Immunogen**

**Species (MHC)** human (B63)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B63 epitope.

**HXB2 Location** Rev (14–23)

**Author Location**

**Epitope** KAVRLIKFLY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Rev (14–28)

**Author Location** (C consensus)

**Epitope** QAVRIKILYQSNPY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Rev (15–23)

**Author Location** Rev (15–23)

**Epitope** TVRLIKFLY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*03)

**Donor MHC** A\*03, A\*24, B\*35, B\*40

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** superinfection, characterizing CD8+ T cells

**References** Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- The response to this epitope, TVRLIKFLY, was present only after superinfection. The epitope from the first infecting strain had the substitutions tvKlikfly relative to the test peptide, while the second strain shared the sequence TVRLIKFLY.

**HXB2 Location** Rev (20–28)

**Author Location** Rev

**Epitope** KILYQSNPY

**Epitope name** 1341

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A02, A03, B08, B51, Cw01, Cw07

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KILYQSNPY: 36%

**HXB2 Location** Rev (25–39)

**Author Location** Rev (25–39 HXB2)

**Epitope** SNPPNPEGTRQARR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human



- References** Blazevic *et al.* 1995
- Induces both Th and CTL activities, no HLA restriction analysis performed.

**HXB2 Location** Rev (33–48)  
**Author Location** Rev (33–48 HXB2)  
**Epitope** GTRQARRRRRRWRER  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Blazevic *et al.* 1995
- Induces both Th and CTL activities, no HLA restriction analysis performed.

**HXB2 Location** Rev (41–56)  
**Author Location** Rev (41–56 HXB2)  
**Epitope** RRRRWRRERQRQIHSIS  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Blazevic *et al.* 1995
- Induces both Th and CTL activities.

**HXB2 Location** Rev (51–59)  
**Author Location** Rev (51–59)  
**Epitope** QIRTYSGWI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A2, B13, B41  
**Country** France  
**Assay type** Other  
**Keywords** computational epitope prediction, escape, acute/early infection, immune evasion  
**References** Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- Epitope QIRTYSGWI did not change in the subjects studied.

**HXB2 Location** Rev (51–60)  
**Author Location** Rev  
**Epitope** QIRSLSGWIL  
**Epitope name** QL10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A2, B44, B7, Cw5, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 7, QIRSLSeWIL was found not to correspond to the most polymorphic residue in the epitope. This is a novel unmapped epitope.

**HXB2 Location** Rev (52–60)  
**Author Location** (C consensus)  
**Epitope** IHSISERIL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1510)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the H2 residue of IHSISERIL are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** Rev (55–63)  
**Author Location** Rev  
**Epitope** ISERILSTY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0101)  
**Donor MHC** A\*0101, A\*0301, B\*0801, B\*5101; A\*0101, B\*0801  
**Country** United Kingdom  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** escape, acute/early infection, characterizing CD8+ T cells  
**References** Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- The second donor in the study shares A\*0101 and B\*0801 with his partner. The escape variant iserilStF was transmitted, and it abrogates binding to A\*0101.

**HXB2 Location** Rev (55–63)  
**Author Location** Rev (55–63 LAI)  
**Epitope** ISERILSTY  
**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Keywords** rate of progression

**References** van Baalen *et al.* 1997

- Predicted to be an HLA-A1 epitope based on anchor residues 2S and 9Y.
- Both forms LSGWL(L or I)STY, with intact anchors, were found in an HLA-A1+ individual with Rev-responsive CTL.
- An HLA-A1 individual who did not make a Rev response had lost the C-term anchor, ISGWILS(T or N)S.
- 3/7 long-term non-progressors and 0/5 progressors were positive for HLA-B57 (associated with prolonged survival)
- CTLp frequencies to Rev and Tat were inversely correlated with rapid progression to AIDS, but not Gag, RT or Nef.

**HXB2 Location** Rev (55–63)

**Author Location** Rev (55–63)

**Epitope** ISERILSTY

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A1)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** Rev (55–63)

**Author Location** RT Pol (55–63)

**Epitope** ISERILSTY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 8/13 patients recognized this epitope, it was the most commonly recognized of three A\*01 epitopes tested.

**HXB2 Location** Rev (55–63)

**Author Location** Rev

**Epitope** ISERILSTY

**Epitope name** A1-IY9(Rev)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.

- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.

- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Rev (56–64)

**Author Location** Rev

**Epitope** SEWILSTHL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A28, A29, B14, B44, Cw8

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 2, SkWILSTHL was found in the most polymorphic residue in the epitope. This is a novel unmapped epitope.

**HXB2 Location** Rev (57–66)

**Author Location** Rev (57–66)

**Epitope** ERLSTYLGR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Rev (57–66)

**Author Location** Rev (57–66)

**Epitope** ERLSTYLGR

**Epitope name** A3-ER10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Rev (57–66)  
**Author Location** Rev  
**Epitope** ERILSTYLGR  
**Epitope name** A3-ER10(Rev)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Rev (57–66)  
**Author Location**  
**Epitope** ERILSTYLGR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** epitope processing, escape  
**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing.

This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.

- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Rev (58–66)  
**Author Location** Rev (58–66)  
**Epitope** RILSTYLGR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**Keywords** early-expressed proteins  
**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Rev (59–75)  
**Author Location** (C consensus)  
**Epitope** ILSTCLGRPAEPVPLQL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1510)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Rev (63–71)  
**Author Location** Rev (63–71)  
**Epitope** YLGSEEPV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A2, B13, B41  
**Country** France  
**Assay type** Other  
**Keywords** computational epitope prediction, escape, acute/early infection, immune evasion  
**References** Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- No variants of epitope YLGGSEEPV were found in the subjects studied.

**HXB2 Location** Rev (66–73)

**Author Location** Rev (66–)

**Epitope** RSAEPVPL

**Epitope name** Rev66

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* Rev  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** transgenic mouse (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a low A2-binder, and induced a CTL responses in 1/6 A2 transgenic mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

**HXB2 Location** Rev (66–75)

**Author Location** Rev (66–75)

**Epitope** RPAEPVPLQL

**Epitope name** RL10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07)

**Assay type** CTL suppression of replication

**Keywords** class I down-regulation by Nef

**References** Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein Rev epitope RPAEPVPLQL-recognizing CTLs were affected by Nef.

**HXB2 Location** Rev (66–75)

**Author Location** Rev (66–75)

**Epitope** RPAEPVPLQL

**Epitope name** RL10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B07)

**Assay type** Chromium-release assay, Other

**Keywords** binding affinity

**References** Bennett *et al.* 2007

- Standard assays like ELISpot, ICS and tetramer staining do not measure antiviral activity of HIV-infected CTLs, but use exogenous synthetic peptides on uninfected cells or HLA tetramers. Similarly, functional avidity assesses CTL activity against uninfected target cells. Here functional avidity is compared to the efficiency of actual infected cells' recognition and killing, revealing a sharp threshold between CTL immune antiviral activity and lack of infected cell recognition.
- As previously shown, epitopes and their variants spanned orders of magnitude of SD50. Likewise, CTL clearance of infected cells varied from 0 to 100% with epitope sequence variation. Moreover, direct suppression of HIV-1 replication by CTLs also varied with epitope variant.
- When killing efficiency (KE) using virus-infected cells was compared to functional avidity using synthetic peptides, there was a narrow threshold separating maximal killing from almost none. Since different SL9-specific clones had similar KEs, which were vastly different from RL10-specific CTL KEs, it was obvious that KEs varied with epitope sequence too. Finally, a strong correlation between KE and inhibition of viral replication was also seen.
- This epitope, RPAEPVPLQL, showed marked differences in its functional avidity, killing efficiency, as well as inhibition of viral replication when compared to its variants RsAEPVPLQL, RPtEPVPLQL, RPeEPVPLQL, RPAqPVPVPLQL, RPAEPVPLhL, RPAEPVPfQL, RPvEPVPLQL, RPeEPVPfQL, RPeEPVPLpL, RPAEPVPfhL, RPtEPVPfQL, RPtEPVPLeL, RPqEPVPLIL and RPtEPVPfhL.

**HXB2 Location** Rev (66–75)

**Author Location**

**Epitope** RPAEPVPLQL

**Epitope name** RL10

**Immunogen**

**Species (MHC)** human (B7)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B07 epitope.

**HXB2 Location** Rev (66–81)

**Author Location** Rev (66–78)

**Epitope** RPAEPVPLQLPPIERL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*13)

**Donor MHC** A\*0301, A\*3001, B\*1301, B\*1402, Cw\*0602, Cw\*0802

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism

**References** Honeyborne *et al.* 2007

- To determine whether HLA-B\*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B\*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B\*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.
- An HLA-B\*13-restricted epitope was found within the above overlapping peptide sequences, but the optimal epitope was not confirmed.

**HXB2 Location** Rev (66–81)

**Author Location** Rev

**Epitope** RSAEPVPLQLPPLERL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot – 36% (25/70) targeted one or more Rev peptides, and this peptide was the most frequently recognized epitope in Rev (32%).
- The regulatory proteins Rev and Tat combined contributed to 3%, and the accessory proteins Vif, Vpr and Vpu to 7%, of the total magnitude of HIV-1 specific CTL responses in a subset of 22 HIV-1 infected individuals in whom all HIV-1 proteins were studied.

**HXB2 Location** Rev (66–81)

**Author Location** Rev

**Epitope** RSAEPAPLQLPPLERL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmaped epitope.
- RSAEPAPLQLPPLERL shows a mutation over time in position 6, RSAEPvPLQLPPLERL.

**HXB2 Location** Rev (67–75)

**Author Location** (LAI)

**Epitope** SAEPVPLQL

**Subtype** B

**Immunogen**

**Species (MHC)** (B14)

**References** van Baalen & Gruters 2000

**HXB2 Location** Rev (67–75)

**Author Location** Rev

**Epitope** SAEPVPLQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** escape

**References** Schutten *et al.* 2001

- Molecularly cloned primary NSI macrophage tropic strain 2.1 and SI non-macrophage tropic strain 1.2 were isolated from study participant ACH320 and used to infect irradiated XID mice that had been reconstituted with human PBMC from B14+ seronegative donors – results indicate CTL may favor selective outgrowth of macrophage tropic strains.
- The CTL clone TCC108 specific for SAEPVPLQL, previously described by van Baalen 1997, and van Baalen 1998, was stimulated *in vitro* and given to the mice to apply specific CTL pressure.
- The macrophage-tropic HIV-1 strain #2.1 escaped CTL pressure more efficiently (7/14 animals) than its non-macrophage-tropic counterpart #1.2(SI) – the latter isolate was suppressed in 13/14 animals – macrophage may serve as a CTL sanctuary and reduced pressure on macrophage tropic HIV strains may allow additional replication to assist with acquisition of escape.
- Specific HIV-1 variants selectively induced by TCC108 were for strain 1.2: SEEPVPLQL, and for strain 2.1: SAEHVPLQL, SAESVPLQL, SVEPVPLQL, SLEPVPLQL, SAEPVPFQL, and SAEPVPFQL.

**HXB2 Location** Rev (67–75)

**Author Location** Rev (67–75)

**Epitope** SAEPVPLQL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** acute/early infection, early-expressed proteins, kinetics

**References** van Baalen *et al.* 2002

- Tat, Rev and Nef are the first HIV proteins expressed upon acute infection of T-cells (< 6 hours), and RT is not expressed until after 24 hours. The B14-restricted Rev-SAEVPLQL specific CD8 T-cell clone TCC108, and the B57-restricted RT-IVLPEKDSW specific CD8 T-cell clone TCL1C11 were co-cultured with CD4+ cultures inoculated with HIV-1 at low MOI. Co-incubation with the Rev-specific CTL resulted in two logs less HIV-1 production in ten days of culture. When the RT epitope was cloned into the Nef gene of the infecting strain, another early expressed protein, it proved as effective as the Rev epitope at inhibiting viral production. A mathematical model of CTL-target interactions suggest early proteins are important for vaccine design.

**HXB2 Location** Rev (67–75)

**Author Location** Rev (67–75)

**Epitope** SAEPVPLQL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Rev (67–75)

**Author Location** Rev

**Epitope** SAEPVPLQL

**Epitope name** B14-SL9(Rev)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Rev (67–75)

**Author Location** Rev (67–75 IIIB)

**Epitope** SAEPVPLQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14, Cw8)

**References** van Baalen *et al.* 1998

- The Rev-specific CTL response studied here was from an individual infected with HIV-1 for more than 12 years without developing symptoms – Rev and Tat are expressed early and CTL activity against these proteins has been correlated with long-term survival.
- The CTL clone TCC108 specific for this epitope was studied *in vitro*.
- CTLs added immediately after infection suppressed viral production, indicative of CTL interference with viral production prior to lysis – CTL-mediated lysis occurred after the onset of progeny viral release, but prior to peak viral production.
- Rapid selection of a E69K mutation, which abolished CTL, recognition was observed.
- The epitope was originally listed as B14, but Cw8 and B14 are in linkage disequilibrium, and in this case were not distinguished (pers. comm., Christian Brander, 1999)

**HXB2 Location** Rev (67–75)

**Author Location** (LAI)

**Epitope** SAEPVPLQL

**Subtype** B

**Immunogen**

**Species (MHC)** human (Cw\*0501)

**Keywords** optimal epitope

**References** Addo *et al.* 2001; Frahm *et al.* 2008

**HXB2 Location** Rev (67–75)

**Author Location** Rev (SF2)

**Epitope** SAEPVPLQL

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw5)

**Keywords** acute/early infection

**References** Goulder *et al.* 2001a

- Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia.
- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation.

**HXB2 Location** Rev (67–75)

**Author Location** Rev (67–75 SF2)

**Epitope** SAEPVPLQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw5)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-Cw5+ individuals that had a CTL response to this epitope broken down by group: 2/6 group 1, 0/1 group 2, and 0/2 group 3.

**HXB2 Location** Rev (67–75)

**Author Location** Rev (67–75)

**Epitope** SAEPVPLQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw5)

**Donor MHC** A\*0201, A1, B44, B57, Cw5, Cw6

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes was characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** Rev (67–75)

**Author Location** Rev (67–75)

**Epitope** SAEPVPLQL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw5)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** escape, optimal epitope

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- Escape occurred at position 5 of this epitope, saepGplql.

**HXB2 Location** Rev (67–75)

**Author Location** Rev

**Epitope** SAEPVPLQL

**Epitope name** SL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw5)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 5, SAEPgPLQL, was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** Rev (67–75)

**Author Location** Rev (67–75)

**Epitope** SAEPVPLQL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw5, Cw8)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Rev (67–75)

**Author Location** Rev (69–77 BRU)

**Epitope** SAEPVPLQL

**Epitope name** Rev SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**Keywords** HAART, ART, supervised treatment interruptions (STI), acute/early infection

**References** Addo *et al.* 2001

- Rev and Tat are expressed early in the virus life cycle and thus may be important targets for CTL against HIV early in infection and for vaccines – therefore CTL responses against Tat and Rev were screened using overlapping peptides.
- 11/57 (19.3%) HIV-1 + individuals recognized at least 1 Tat peptide, and 21/57 (37%) responded to at least 1 Rev peptide.
- This epitope is the first HIV-specific CTL epitope restricted by HLA-Cw5.
- This epitope was recognized by 2/5 individuals expressing HLA-Cw8 and by 5/11 individuals expressing Cw5 allele, which differs from Cw8 by 4 amino acids, suggesting promiscuous presentation of the epitope between those HLA molecules.
- Longitudinal data was available for 6 Rev-SL9 responders, who were treated during acute infection, and the response was stable 2 and 12 months after initiation of HAART, measurements by ELISPOT and flow-based intracellular cytokine staining (ICS) were concordant – in two subjects the response was heightened by transient reexposure to antigen with treatment interruption at 12 to 14 months.

**HXB2 Location** Rev (67–75)

**Author Location** Rev

**Epitope** SAEPVPLQL

**Epitope name** Cw8-SL9(Rev)

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Rev (67–75)

**Author Location**

**Epitope** SAEPVPLQL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
- What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Rev (67–75)

**Author Location** Rev (65–77 BH10, LAI)

**Epitope** SAEPVPLQL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is GRSAEPV-PLQLPP) has similarity with transforming growth factor beta binding protein protein I, fragment ARSAEPEVATAPP.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is EPV-PLQLPPL) also has similarity with the epidermal growth factor receptor substrate 15, fragment EPVMSLPPA.

**HXB2 Location** Rev (67–75)

**Author Location** Rev (67–75)

**Epitope** SAEPVPLQL

**Immunogen** HIV-1 infection, in vitro stimulation or selection

**Species (MHC)** human

**Assay type** HLA binding

**Keywords** assay standardization/improvement, characterizing CD8+ T cells

**References** van Baalen *et al.* 2005

- A new sensitive, non-radioactive assay, called fluorescent antigen-transfected target cell-CTL (FATT-CTL) assay, was developed to measure antigen-specific cytotoxicity *ex vivo*. Target cells were generated by nucleofection with DNA vectors encoding antigen-GFP fusion proteins. Flow cytometry was used to quantify viable and dead GFP-positive cells after coculture with different effector:target cell ratios. Cytotoxicity was detected at lower effector:target cell ratios than in standard Cr-release assay. Antigen-specific cytotoxicity was detected *ex vivo* in PBMCs from HIV-1 infected individuals.

**HXB2 Location** Rev (70–78)

**Author Location** Rev (70–78)

**Epitope** PVPFQLPPL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A2, B13, B41

**Country** France

**Assay type** Other

**Keywords** computational epitope prediction, escape, acute/early infection, immune evasion

**References** Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- The previously described epitope PVPFQLPPL, had a variant PVPIQLPPL in the fourth position.

**HXB2 Location** Rev (72–88)

**Author Location** (C consensus)



- Epitope** PLQLPPIERLHIDCSES  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*13)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HXB2 Location** Rev (73–81)  
**Author Location** Rev (73–81)  
**Epitope** LQLPPLERL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007
- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
  - This epitope, LQLPPLERL, was detected within overlapping peptide PLQLPPLERLTLDCNED.
- HXB2 Location** Rev (73–81)  
**Author Location** Rev (73–)  
**Epitope** LQLPPIERL  
**Epitope name** Rev73  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* peptide *HIV component:* Rev  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)  
**Species (MHC)** human, transgenic mouse (A2)  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction  
**References** Corbet *et al.* 2003
- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL responses in mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.
- HXB2 Location** Rev (74–82)  
**Author Location** Rev (74–82)  
**Epitope** QLPPLERLT  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A2, B13, B41  
**Country** France  
**Assay type** Other  
**Keywords** computational epitope prediction, escape, acute/early infection, immune evasion  
**References** Guillon *et al.* 2006
- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
  - Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
  - No variants of epitope QLPPLERLT were found in the subjects under study.
- HXB2 Location** Rev (75–83)  
**Author Location**  
**Epitope** LPPLERLTL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** epitope processing, escape  
**References** Yusim *et al.* 2002
- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
  - While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
  - In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.
  - What was learned from proteins where many epitopes have been defined (Gag, Pol, Env and Nef) was used to develop an algorithm to predict where epitopes would be localized in Rev, Tat, Vif, and Vpr. Predictions were made blinded, and then compared to the first 15 epitopes defined in these proteins; the epitopes were concentrated in the predicted regions.

**HXB2 Location** Rev (96–104)  
**Author Location** Rev (96–)  
**Epitope** GMGSPQILV  
**Epitope name** Rev96(2M)  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* peptide *HIV component:* Rev  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder, and induced a CD8+ T-cell IFN gamma response in 1/6 mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.
- The variant gVgspqilv did not elicit a CD8+ T-cell IFN gamma response in transgenic mice, and bound to A2 with low affinity.

**HXB2 Location** Rev (98–116)  
**Author Location** Rev  
**Epitope** GSTQVSVESPTVLEPGTKE  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A28, A29, B14, B44, Cw8  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope. A P->L change occurred in a patient that recognized this peptide, over time: GSTQVSVESITVLEPGTKE

**HXB2 Location** Rev (101–109)  
**Author Location** Rev (101–109)  
**Epitope** QILGEPPTV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A2, B13, B41  
**Country** France  
**Assay type** Other

**Keywords** computational epitope prediction, escape, acute/early infection, immune evasion

**References** Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- The previously described epitope QILGEPPTV, contained variants QILGEhPpV in the sixth and eighth positions and QILGghPpV in the fifth, sixth and eighth positions.

**HXB2 Location** Rev (101–110)  
**Author Location** Rev  
**Epitope** QVLGESPTVL  
**Epitope name** QL10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A11, A2, B18, B44, Cw12, Cw5  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Two escape mutations, at positions 5 and 7, QVLGkSPTVL and QVLGESfTVL, were found not to correspond to the most polymorphic residues in the epitope. This is a novel unmapped epitope.

**HXB2 Location** Rev (102–110)  
**Author Location** Rev (102–110)  
**Epitope** ILVESPAVL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method

of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.

- This epitope, ILVESP AVL, was detected within overlapping peptide TQGVGSPQILVESP AVL.

**HXB2 Location** Rev (102–110)

**Author Location** Rev (102–)

**Epitope** ILVESP AVL

**Epitope name** Rev102

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* Rev  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder that did not induce CTL or CD8+ T-cell IFN gamma responses in mice, but responses were detected in 2/17 HIV+ HLA-A2 subjects.

**HXB2 Location** Rev (102–110)

**Author Location** Rev (102–110)

**Epitope** ILGEPPTVL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A2, B13, B41

**Country** France

**Assay type** Other

**Keywords** computational epitope prediction, escape, acute/early infection, immune evasion

**References** Guillon *et al.* 2006

- A longitudinal study from primary infection to 5 years postinfection was conducted to determine Tat and Rev gene evolution. 2/4 patients showed Tat gene evolution. It was found that though Tat evolved by mostly nonsynonymous, non-random sequence changes, there was no increase in transactivating capacity or size of Tat protein. Sequence evolution occurred mostly in predicted epitopes that are MHC I restricted.
- Tat and Rev seem to evolve due to CTL pressure later in infection, after seroconversion, and possibly during viral replication.
- The previously described epitope ILGEPPTVL varied to ILGEhPhVL in the fifth and seventh positions and ILGghPhVL in the fourth, fifth and seventh positions.

**HXB2 Location** Rev (107–116)

**Author Location** Rev

**Epitope** PTVLESGTKE

**Epitope name** 1277

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A68)

**Donor MHC** A11, A68, B42, B45, Cw16, Cw17

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for PTVLESGTKE:16%. This epitope can be presented by A68, but did not bind to A11.

**HXB2 Location** Rev

**Author Location** Rev

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor with cationic liposome *HIV component:* gp160, Rev

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Ishii *et al.* 1997

- pCMV160/Rev is a DNA vaccine candidate carrying gp160 and Rev linked to a cytomegalovirus (CMV promotor)
- pCMV160/Rev given in conjunction with a cationic liposome gave enhanced DTH, Ab and CTL responses.

**HXB2 Location** Rev

**Author Location** Rev

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Rev  
*Adjuvant:* CD40

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** Th1, Th2

**References** Ihata *et al.* 1999

- pcRev DNA i.m. vaccination in BALB/c mice induced Th1, Th2 and IgG responses, and enhanced the CTL response to Rev, but did not induce mucosal IgA.

**HXB2 Location** Rev

**Author Location** Rev

**Epitope**

**Immunogen** vaccine

*Vector/Type:* adeno-associated virus (AAV)  
*HIV component:* Env, Rev, Tat *Adjuvant:* IL-2

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Xin *et al.* 2001

- An AAV vector expressing HIV-1 env, tat, and rev genes (AAV-HIV vector) was used to vaccinate BALB/c mice.

- A single injection stimulated and long lasting serum IgG, fecal IgA, and HIV-specific CTL.
- Boosting enhanced the humoral response, and IL2 enhanced T-cell immunity.

**HXB2 Location** Rev

**Author Location** Rev

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Nef, Rev, Tat

**Species (MHC)** human

**Keywords** HAART, ART

**References** Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-gamma production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

**HXB2 Location** Rev

**Author Location** (subtype C)

**Epitope**

**Subtype** C

**Immunogen**

**Species (MHC)** human

**References** Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- Anti-Rev CTL responses were distributed throughout the protein and 27 of 47 subjects (57%) demonstrated HIV-1C Rev-specific ELISPOT CTL responses of more than 100 SFC/106 PBMC.

**HXB2 Location** Rev

**Author Location** Rev

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)

**Species (MHC)** human

**Keywords** review

**References** Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on the stimulatory role of CpG motifs and how HIV-1 DNA vaccines can boost the CTL and Th proliferative responses in asymptomatic HIV+ individuals.

**HXB2 Location** Rev

**Author Location** Rev

**Epitope**

**Immunogen** HIV-1 infection, vaccine

**Species (MHC)** human

**Keywords** review, escape, early-expressed proteins

**References** Gruters *et al.* 2002

- This paper is a review that makes a case for using Tat and Rev as part of a vaccine strategy.
- CTL against Tat and Rev were found preferentially in long term non-progressors.
- Tat/Rev vaccinations of macaques provided protection or reduction in viremia, with high levels of CTL providing protection from challenge, lower levels of CTL having lower viremia, while Gag/Pol vaccinations with did not result in decreased viremia.
- Early expression of Tat/Rev may in part explain the enhanced benefit of a CTL response directed at these proteins, and CTL escape is more prominent in these proteins.

**HXB2 Location** Rev

**Author Location** Rev

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** T-cell Elispot

**References** Wang *et al.* 2006

- The association between T cell response and CD4+ T cell counts or CD4+ was investigated, using overlapping peptides corresponding to natural B clade and C consensus sequences.
- T cell responses and CD4+ count were correlated for Gag p24 and Gag p17 (B and C clades) and for Pol (C clade). CD4+ counts were higher in patients with Tat and /or Rev T cell response than in patients without Tat and Rev response.

## II-B-20 Vpu CTL/CD8+ epitopes

**HXB2 Location** Vpu (4–13)

**Author Location** Vpu

**Epitope** LVILAIIVALV

**Immunogen**

**Species (MHC)** human (B7)

**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes could stimulate IFN $\gamma$  production in an ELISPOT assay.
- LVILAIIVALV was newly identified as an HLA-B7 epitope in this study using ELISPOT, but could not be shown to bind to B7.

**HXB2 Location** Vpu (4–13)

**Author Location** Vpu

**Epitope** LVILAIIVALV

**Epitope name** 1300

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A03, A24, B07, B38, Cw07, Cw12/13

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for LVILAIVALV: 6%

**HXB2 Location** Vpu (7–15)

**Author Location** Vpu (7–15)

**Epitope** LAIVALVVA

**Subtype** B

**Immunogen** HIV-1 infection, peptide-HLA interaction

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** immunodominance

**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, LAIVALVVA, is similar to human protein Trypsin-domain protein, sequence aVALVVApL, and human small inducible cytokine 28 protein, sequence LAIVALaV.

**HXB2 Location** Vpu (13–21)

**Author Location** Vpu (13–)

**Epitope** VVAATIAIV

**Epitope name** Vpu13

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* Vpu

*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder that did not induce CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

**HXB2 Location** Vpu (25–40)

**Author Location** Vpu

**Epitope** IVFIEYRKLQRKID

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot – only 2% (2/70) targeted one or more Vpu peptides, including this peptide.
- The regulatory proteins Rev and Tat combined contributed to 3%, and the accessory proteins Vif, Vpr and Vpu to 7%, of the total magnitude of HIV-1 specific CTL responses in a subset of 22 HIV-1 infected individuals in whom all HIV-1 proteins were studied.

**HXB2 Location** Vpu (29–37)

**Author Location** Vpu (29–37)

**Epitope** EYRKILRQR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3303)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002b

- CTL responses against regulatory and accessory proteins in 70 HIV-1 infected patients were studied using overlapping peptides and Elispot.
- 28% targeted one or more overlapping Tat peptides; 36%, Rev peptides; 33%, Vif peptides; 40%, Vpr peptides; and 2%, Vpu peptides.
- All known optimally defined epitopes were summarized for the five proteins.

**HXB2 Location** Vpu (29–37)

**Author Location** Vpu (29–37)

**Epitope** EYRKILRQR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3303)

**Keywords** early-expressed proteins

**References** Addo *et al.* 2002a

- Detection of HIV CTL epitopes is rare in Vpu, and this is the first optimally defined Vpu epitope.
- This CTL response was first detected in a long term non-progressor, and 3/6 HLA A\*3303 positive individuals were found to have a CTL response to this epitope.
- HLA A\*3303 is common in West Africa and Asia.

**HXB2 Location** Vpu (29–37)  
**Author Location** Vpu (29–37)  
**Epitope** EYRKILRQR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3303)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Vpu (29–43)  
**Author Location**  
**Epitope** EYRKILRQRKIDRLI  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade MN *HIV component:* gp160

**Species (MHC)** human  
**Donor MHC** A1, A33; B44, B8  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes  
**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85–86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Vpu (62–82)  
**Author Location** Vpu (65–81)  
**Epitope** AALVEMGHDAPWVDDL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A2, B44, B7, Cw5, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope. The third position was found to vary over time to AAFVEMGHDAPWVDDL.

**HXB2 Location** Vpu (66–82)  
**Author Location** (C consensus)  
**Epitope** STMVDMGHLRLLDVNDL  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*6801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** Vpu (74–82)  
**Author Location** Vpu (74–82 2001 HIV-1 subtype B cons)

**Epitope** HAPWDVNDL  
**Epitope name** HL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*0102)  
**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape, immune evasion, optimal epitope  
**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Last position (9) in the epitope had potentially experienced positive selection. HAPWD-VNDm escape variant was found.

**HXB2 Location** Vpu  
**Author Location** Vpu  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Nef, Vif, Vpu  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Keywords** subtype comparisons, Th1  
**References** Ayyavoo *et al.* 2000

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN-gamma levels.
- Antigen stimulation increased IFN-gamma production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization-stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

## II-B-21 gp160 CTL/CD8+ epitopes

**HXB2 Location** gp160 (2–10)  
**Author Location** gp160 (2–10 IIIB)  
**Epitope** RVKEYQHL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0801 epitope.

**HXB2 Location** gp160 (2–10)  
**Author Location** gp160 (2–10 IIIB)  
**Epitope** RVKEYQHL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Keywords** subtype comparisons  
**References** Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- Type-specific epitope, unique to the LAI and IIIB because of a deletion of three amino acids that are present in all other subtype B HIV-1s.
- RVKGIRKNYQHL, a variant found in JRCSF, was not recognized.
- This epitope is in the signal sequence of gp120.

**HXB2 Location** gp160 (2–10)  
**Author Location** gp120 (2–10)  
**Epitope** RVKEYQHL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

**HXB2 Location** gp160 (2–10)  
**Author Location**  
**Epitope** RVKEYQHL  
**Immunogen**  
**Species (MHC)** (B8)

**Keywords** review, immunodominance, escape, vaccine antigen design

**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

**HXB2 Location** gp160 (6–12)  
**Author Location** gp120 (6–15 CM243 subtype CRF01)  
**Epitope** TQMNWPNLWK  
**Epitope name** E6-15  
**Subtype** CRF01\_AE

**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope after a second stimulation *in vitro* gave a weak response in HEPS study subject 186 who was HLA A2/A11.

**HXB2 Location** gp160 (6–12)  
**Author Location** gp120 (6–15 CM243 subtype CRF01)  
**Epitope** TQMNWPNLWK  
**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Keywords** subtype comparisons  
**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it.
- This epitope was not conserved in other subtypes, and exact matches were rare.

**HXB2 Location** gp160 (30–40)  
**Author Location** Env (29–39)  
**Epitope** AAENLWVTVYY

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load..
- Less than 2 of 11 patients recognized this epitope.

**HXB2 Location** gp160 (30–40)  
**Author Location** gp160  
**Epitope** AENLWVTVYY  
**Epitope name** B44-AY10(gp160)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (30–46)

**Author Location** Env

**Epitope** AAENLWVTVYYGVPVWK

**Epitope name** ENV-05

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, aaeNLWVTVYYGVPVWK differs from the consensus C sequence vggNLWVTVYYGVPVWK at 3 amino acid positions, i.e. by 17.6%.

**HXB2 Location** gp160 (30–49)

**Author Location** gp120

**Epitope** AAEQLWVTVYYGVPVWKEAT

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** TCR usage

**References** Weekes *et al.* 1999b

- Peptide 7035.1: Almost all CD8+ T cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed in the CD28 depleted cell population.
- HIV CTL responses to 3 Env and 2 Gag peptides were studied.
- The clonal composition of the TCR V $\beta$  responses was studied and was found to be highly focused, with one TCR beta-chain sequence tending to dominate the peptide-specific response – clones to this epitope were V $\beta$ 6.

**HXB2 Location** gp160 (30–49)

**Author Location** gp120 (30–49)

**Epitope** AAEQLWVTVYYGVPVWKEAT

**Epitope name** Peptide 7035.1

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A29, B44, B8

**Country** United Kingdom

**Assay type** Flow cytometric T-cell cytokine assay, Other

**Keywords** HAART, ART, immunodominance, TCR usage, memory cells

**References** Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintenance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

**HXB2 Location** gp160 (30–49)

**Author Location** gp120 (1–20)

**Epitope** ATEKLWVTVYYGVPVWKEAT

**Epitope name** ATE

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, escape

**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant epitopes increased using



PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.

- This was one of 8 reactive peptides found not to vary over time. It was one of four epitopes that were not precisely defined.

**HXB2 Location** gp160 (31–39)

**Author Location**

**Epitope** AENLWVTVY

**Epitope name** AY9

**Immunogen**

**Species (MHC)** human (B\*1801)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1801 epitope.

**HXB2 Location** gp160 (31–39)

**Author Location** gp120 (31–39 HIV-MN)

**Epitope** AENLWVTVY

**Epitope name** AY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1801)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Position 1 in the epitope had potentially experienced positive selection. AdNLWVTVY, tDNLWVTVY, tEdLWVTVY, eEdLWVTVY and AEdsWVTVY escape variants were found.

**HXB2 Location** gp160 (31–39)

**Author Location** gp160 (30–38 WEAU)

**Epitope** AENLWVTVY

**Epitope name** gp160 AY9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4403)

**Donor MHC** A\*2902, B\*0801, B\*4403

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- This was the immunodominant response in acute infection in WEAU, and there was rapid escape in the epitope AENLWVTVY, with three variants observed by day 30 from the onset of symptoms. Additional mutations continued to develop, so that there were 9 different forms observed through the course of sampling. The variants all conferred different levels of reduction in CTL response, double mutations or anchor mutations tended to cause the greatest reduction: AaNLWV-TaY, tNkWVTVY, AgNLWVTVY, AkNLWVTVY, although the double mutant tENLWVTiY elicited a very strong CTL response, suggesting it might not be an escape form.

**HXB2 Location** gp160 (31–39)

**Author Location** gp120 (30–38 SF2)

**Epitope** AENLWVTVY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B44+ individuals that had a CTL response to this epitope broken down by group: 1/8 group 1, 2/3 group 2, and 3/4 group 3.

**HXB2 Location** gp160 (31–39)

**Author Location** gp120 (30–38)

**Epitope** AENLWVTVY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B44)

**References** Day *et al.* 2001

**HXB2 Location** gp160 (31–39)

**Author Location** gp120**Epitope** AENLWVTYV**Immunogen** HIV-1 infection**Species (MHC)** human (B44)**Keywords** epitope processing**References** Cao *et al.* 2002

- AC2 is a B44 restricted CTL clone that recognizes AENLWVTYV.
- CTL could be activated by a fusion protein of an HIV protein and anthrax lethal factor (LFn-HIV) that promotes antigen presenting cell uptake of exogenous protein and allows processing through the MHC class I pathway. This strategy for CTL detection could allow antigen presentation without generation of cells by the standard methods of using live viral vectors carrying a protein, or by loading the cells with peptides and by-passing processing.

**HXB2 Location** gp160 (31–39)**Author Location** (B consensus)**Epitope** AENLWVTYV**Epitope name** AY9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B44)**Donor MHC** A11, A29, B08, B44, Cw4, Cw7**Country** United States**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells**References** Lichtenfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** gp160 (31–39)**Author Location****Epitope** AENLWVTYV**Epitope name** AY9**Immunogen****Species (MHC)** human (B44)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a B44 epitope.

**HXB2 Location** gp160 (31–39)**Author Location****Epitope** AENLWVTYV**Immunogen** HIV-1 infection**Species (MHC)** human (B44)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** binding affinity, immunodominance, optimal epitope**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope AENLWVTYV elicited a magnitude of response of 160 SFC with a functional avidity of 5nM.

**HXB2 Location** gp160 (31–39)**Author Location** gp160 (31–39)**Epitope** AENLWVTYV**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A1, A29, B44, B8**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** HAART, ART, escape, viral fitness and reversion**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, AENLWVTYV, was found to be 0.048/day (upper bound on rate of escape = 0.053), with SE of 0.022.
- Mutations at position 30 (E30G and E30A) were shown to confer escape.

**HXB2 Location** gp160 (31–40)**Author Location** gp160 (30–39 WEAU)**Epitope** AENLWVTYYY**Immunogen** HIV-1 infection**Species (MHC)** human (B\*4402)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*4402 epitope.

**HXB2 Location** gp160 (31–40)**Author Location** gp160 (30–39 WEAU)**Epitope** AENLWVTYYY

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B44)  
**Keywords** immunodominance, escape  
**References** Borrow *et al.* 1997; Borrow & Shaw 1998; Goulder *et al.* 1997a
- Two CTL lines from the patient WEAU were studied – one had an optimal peptide of (A)AENLWVTVYY, and the other (A)AENLWVTVY, and both responded equally well with one or two N-term Alanines.
  - Rapidly post-infection, a strong immunodominant response was observed against this epitope.
  - The naturally occurring forms of the peptide found in WEAU were tested as targets for early WEAU CTLs – the form TENLWVTVY was as reactive as the wild type AENLWVTVY – but the forms AKNLWVTVY, AGNLWVTVY, AANLWVTVY did not serve as targets.
  - The glutamic acid in the second position is a B44 anchor residue.
  - Goulder *et al.* [1997a] and Borrow & Shaw [1998] are reviews of immune escape that summarizes this study in the context of CTL escape to fixation.

**HXB2 Location** gp160 (31–55)  
**Author Location** gp120 (32–56 LAI)  
**Epitope** TEKLWVTVYYGVPVWKEATTLFCA  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (MHC)** human (B18)  
**References** Johnson *et al.* 1994a

- HLA restricted CTL response to epitope in HIV-1 vaccinia-env vaccinees.

**HXB2 Location** gp160 (31–55)  
**Author Location** gp120 (32–56 LAI)  
**Epitope** TEKLWVTVYYGVPVWKEATTLFCA  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (MHC)** human (B18)  
**References** Ferris *et al.* 1999; Hammond *et al.* 1995

- This peptide can be processed for HLA-B18 presentation by both TAP-1/2 independent and dependent pathways.

**HXB2 Location** gp160 (32–40)  
**Author Location** Env (92TH023)  
**Epitope** DNLWVTVYY  
**Subtype** B, CRF01\_AE  
**Immunogen** vaccine  
*Vector/Type:* canarypox prime with gp120 boost, canarypox, canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Pol  
**Species (MHC)** human (B44)  
**Country** Thailand  
**Assay type** Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Paris *et al.* 2004

- 21% (40/187) of Thai adults that received ALVAC-HIV with or without gp120 or oligomeric gp160 had a CD8+ T-cell response. HLA-B44 was positively associated with CTL responses, and A33 had a borderline significance association with response. A33/B44/DRB1\*0701 is the most common haplotype in Thailand. B46, present in 30% of the population, was negatively associated with CTL responses, although it did not reach significance. HLA class I serotypes A11, A24, A33, B46 and B75 were the most common found in 245 Thai volunteers.
- 9/11 cases of pCTL activity to Env were in people with B44. The authors suggest some of the response may be directed at the previously mapped B44 Env epitope AENLWVTVYY in HXB2, DNLWVTVYY in their CRF01 ALAVC vaccine 92TH023. B\*4403 is the most common B44 allele among Thais, while B\*4402 is more common among Caucasians; a prior study had shown that B\*4403 may be able to present a broader spectrum of epitopes than B\*4402.

**HXB2 Location** gp160 (32–40)  
**Author Location** gp160 (29–37 SUMA)  
**Epitope** ENLWVTVYY  
**Epitope name** GP160 EY9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** gp160 (33–42)  
**Author Location** Env (32–41 subtype B)

**Epitope** KLWVTVYYGV**Subtype** B**Immunogen** HIV-1 infection, vaccine*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160**Species (MHC)** human (A\*0201)**Keywords** binding affinity**References** Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

**HXB2 Location** gp160 (33–42)**Author Location** Env**Epitope** KLWVTVYYGV**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A\*02/A2.1 restricted epitope, KLWVTVYYGV was mutated to nWVTVYYGV in the daughter D2 isolate.

**HXB2 Location** gp160 (33–42)**Author Location** gp120 (33–42)**Epitope** NLWVTVYYGV**Immunogen****Species (MHC)** (A02)**Keywords** subtype comparisons, viral fitness and reversion**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 37/51 Brazilian HIV sequences; present in 100% of subtype C and F sequences.

**HXB2 Location** gp160 (33–42)**Author Location** gp120 (32–41 LAI)**Epitope** KLWVTVYYGV**Subtype** B**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160**Species (MHC)** human (A2)**References** Dupuis *et al.* 1995

- CTL from HLA-A2 positive subject react with this peptide.

**HXB2 Location** gp160 (33–42)**Author Location** Env**Epitope** NLWVTVYYGV**Epitope name** 1256**Subtype** multiple**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Donor MHC** A02, A30, B39**Country** United States**Assay type** T-cell Elispot**Keywords** binding affinity, computational epitope prediction**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for NLWVTVYYGV: 84%

**HXB2 Location** gp160 (34–42)**Author Location****Epitope** LWVTVYYGV**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201)**Assay type** Cytokine production, proliferation, Tetramer binding, Intracellular cytokine staining, Chromium-release assay**References** Dagarag *et al.* 2003

- Telomere length is short in the CD8+ T-cell compartment of HIV-1 infected people, indicating excessive CTL activation and premature senescence. Here human telomerase RT (hTERT) transduction of HIV-1-specific CTL was used to study the functional impact of telomerase. Telomerase expression enhanced proliferative capacity, as well as cytolytic and antiviral capabilities; cytokine production was unchanged. hTERT transduced CTLs were 10-fold more efficient in controlling HIV-1 replication in culture. Thus telomerase transduction can restore CTL mediated cytolysis, and may have therapeutic potential.
- Three polyclonal CD8+ T-cell lines derived from an HIV-1, HLA A\*0201 positive patient were used in this study, including one specific for this epitope.

**HXB2 Location** gp160 (34–42)

**Author Location** gp120 (34–42)

**Epitope** LWVTVYYGV

**Immunogen**

**Species (MHC)** (A\*0201)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 50/51 Brazilian HIV sequences.

**HXB2 Location** gp160 (34–55)

**Author Location** Env

**Epitope** LWVTVYYGVPVWKEATTLFCA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell ELISpot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.

- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A\*02 restricted epitope, LWVTVYYGVPVWKEATTLFCA was mutated to wWVTVYYGVPVWKEATnTLFCA in the daughter D2 isolate.

**HXB2 Location** gp160 (34–55)

**Author Location** gp120 (25–46 BRU)

**Epitope** LWVTVYYGVPVWKEATTLFCA

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Dadaglio *et al.* 1991

- Defined through peptide blocking of CTL activity, and Env deletions.

**HXB2 Location** gp160 (36–44)

**Author Location** gp120 (36–44)

**Epitope** VTVYYGVPV

**Immunogen**

**Species (MHC)** (A02)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 51/51 Brazilian HIV sequences.

**HXB2 Location** gp160 (36–44)

**Author Location** Env (35–)

**Epitope** VTVYYGVPV

**Epitope name** Env35

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* Env

*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human (A2)

**Assay type** CD4 T-cell ELISpot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced a CD8+ T-cell IFN gamma response in 1/6 mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

**HXB2 Location** gp160 (36–46)

**Author Location** Env

**Epitope** VTVYYGVPVWK

**Epitope name** Env 47

**Subtype** M

**Immunogen** vaccine, *in vitro* stimulation or selection, computer prediction

**Vector/Type:** DNA, peptide **Adjuvant:** Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, mouse (A\*1101)

**Assay type** Cytokine production, T-cell Elispot

**Keywords** subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization

**References** McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A\*0201 and A\*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- A total of 9 variant forms of Env 47 were identified. More than 95% of the variant epitopes were recognized by CTLs from mice immunized with the parental form.
- Env 47 epitope (parent or variant form) was present in 82% of HIV sequences of many M group subtypes.

**HXB2 Location** gp160 (36–46)

**Author Location** gp120 (36–46)

**Epitope** VTVYYGVPVWK

**Immunogen**

**Species (MHC)** (A\*6801)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 47/51 Brazilian HIV sequences.

**HXB2 Location** gp160 (36–46)

**Author Location** gp120 (36–46 CM243 subtype CRF01)

**Epitope** VTVYYGVPVWR

**Epitope name** E36-4

**Subtype** CRF01\_AE

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope after a second stimulation *in vitro* gave a weak response in HEPS study subject 186 who was HLA A2/A11.

**HXB2 Location** gp160 (36–46)

**Author Location** gp120 (36–46 CM243 subtype CRF01)

**Epitope** VTVYYGVPVWR

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was not predicted by the EpiMatrix method to be likely to bind to A11, though it served as an epitope in the FSWs, and it was one of the six A11 epitopes that had been previously defined.
- 1/8 tested FSWs recognized this epitope.
- This epitope was only conserved in CRF01 and subtypes B and C, and exact matches were uncommon.

**HXB2 Location** gp160 (36–46)

**Author Location** gp120

**Epitope** VTVYYGVPVWK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6801, A11)

**References** Threlkeld *et al.* 1997

- Study of the fine specificity of an A3-like-HLA-super-type epitope (the A3-super-type includes A\*0301, A\*1101, A\*3101, A\*3301, and A\*6801)
- The A3 super-type is characterized as a hydrophobic or hydroxyl containing anchor residue at position 2, and a positive charge in the C-term position.
- While most lines were specific, a promiscuous cloned CTL line was derived from an HIV+ donor that could recognize this epitope presented by either A11 or A\*6801.

**HXB2 Location** gp160 (37–45)

**Author Location** gp120 (37–45)

**Epitope** TVYYGVPVW

**Epitope name** TW9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*03, A\*11, B\*03)

**Country** Kenya

**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement

**References** McKinnon *et al.* 2007

- The authors suggest that epitope variation has different effects on the HIV- specific immune responses of effector memory T cells (Tem) and central memory T cells (Tcm). They show a lack of correlation between IFN-gamma ELISPOT (Tem typical) and proliferation (Tcm typical) assays for specific epitopes in subjects. Since proliferating CTL also correlate with high intracellular IFN-gamma levels, they surmise that proliferating Tcm differentiate to express Tem functions.
- They also show that proliferating CTL numbers correlate with higher CD4 cell counts.

- Several patients responded strongly to epitope variants that were not part of their autologous HIV-1 sequences. Thus they suggest more comprehensive functional characterizations than the usual overnight IFN-gamma ELISPOTs as well as assessments of Tem versus Tcm specific responses rather than general CTL immune responses.
- 4 variants of this index epitope TVYYGVPVW, TW9, were tested - TiYYGVPVW, TVYYGiPVW, TVYYGVPPrW, TVYYGVPmW. This index peptide, TW9, and its variants show a high proportion of instances where IFN-gamma ELISPOT and proliferation correspond well.

**HXB2 Location** gp160 (37–45)  
**Author Location** gp160  
**Epitope** TVYYGVPVW  
**Subtype** A, B, C, D  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus  
*HIV component:* Env  
**Species (MHC)** human  
**Donor MHC** A\*2902A\*2902, B\*1503, B\*1801, Cw\*0202, Cw\*1203; A\*3001, A\*6601, B\*5703, B\*5801, Cw\*0401, Cw\*1801  
**Country** Kenya  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization  
**References** McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. TVYYGVPVW responses were detected in 2 women who reacted to all clades tested, A, B, C, and D, and the sequence was identical in all clades.

**HXB2 Location** gp160 (37–46)  
**Author Location** gp120 (37–46 LAI)  
**Epitope** TVYYGVPVWK  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (MHC)** human (A\*0301)  
**References** Johnson *et al.* 1994b

- Multiple CTL clones obtained from two vaccinees.
- C. Brander notes that this is an A\*0301 epitope in the 1999 database.

**HXB2 Location** gp160 (37–46)

**Author Location** gp120 (38–41 LAI)  
**Epitope** TVYYGVPVWK  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (MHC)** human (A\*0301)  
**References** Johnson *et al.* 1994a

- Highly conserved epitope recognized by multiple CTL clones from vaccinee.

**HXB2 Location** gp160 (37–46)  
**Author Location** gp120 (37–46 LAI)  
**Epitope** TVYYGVPVWK  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (MHC)** human (A\*0301)  
**References** Ferris *et al.* 1999; Hammond *et al.* 1995

- This peptide can be processed for HLA-A3.1 presentation by TAP-1/2 independent and dependent pathways.

**HXB2 Location** gp160 (37–46)  
**Author Location** gp120 (37–46 LAI)  
**Epitope** TVYYGVPVWK  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (MHC)** human (A\*0301)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0301 epitope.

**HXB2 Location** gp160 (37–46)  
**Author Location** gp120 (37–46 LAI)  
**Epitope** TVYYGVPVWK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**Keywords** acute/early infection  
**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWIIIGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.

- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PIIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** gp160 (37–46)

**Author Location** gp120

**Epitope** TVYYGVPVWK

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade HIV component: p17 Gag, p24 Gag

**Species (MHC)** human (A\*0301)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** gp160 (37–46)

**Author Location** gp120 (430–440)

**Epitope** TVYYGVPVWK

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus HIV component: Gag

**Species (MHC)** human (A\*0301)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** vaccine antigen design

**References** Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated

by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.

- 3/5 subjects with CD8+ T-cell responses responded to this epitope.

**HXB2 Location** gp160 (37–46)

**Author Location** gp120 (37–46)

**Epitope** TVYYGVPVWK

**Immunogen**

**Species (MHC)** (A\*0301, A\*6801)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 47/51 Brazilian HIV sequences.

**HXB2 Location** gp160 (37–46)

**Author Location** Env

**Epitope** TVYYGVPVWK

**Immunogen** vaccine

*Vector/Type:* DNA

**Species (MHC)** transgenic mouse (A11)

**References** Ishioka *et al.* 1999

- A minigene vaccine construct encoding 6 HLA 2.1 and 3 HLA A11 restricted CTL epitopes, the universal Th cell epitope PADRE (pan-DR epitope) and an ER translocating signal sequence was constructed.
- The epitopes were chosen for dominant recognition by CTLs during HBV and HIV infections in humans.
- HLA transgenic mice were used for quantitating *in vivo* immunogenicity of DNA vaccines encoding HLA-restricted CTL epitopes.

**HXB2 Location** gp160 (37–46)

**Author Location** Env

**Epitope** TVYYGVPVWK

**Epitope name** 1283

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6801, A11, A2, A3, B18)

**Donor MHC** A25, A68, B18, B27; A03, A11, B14, B51, Cw08, Cw13

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for TVYYGVPVWK: 18% Promiscuous epitope binding to A02, A03, A11, A6801 and B18.



**HXB2 Location** gp160 (37–46)  
**Author Location** gp120 (37–46)  
**Epitope** TVYYGVPVWK  
**Immunogen** vaccine  
*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease  
**Species (MHC)** human (A3)  
**References** Carruth *et al.* 1999

- The vaccine used was a live recombinant canarypox (CP) virus vaccine containing multiple HIV-1 genes (HIV-1 MN gp120, HIV-1 LAI gp41, HIV-1 LAI Gag, HIV-1 LAI protease)
- CD4+ and CD8+ Gag and Env specific CTL responses were detected in only 1/5 vaccinated volunteers, and were not detectable 1 year after vaccination.
- CTL responses to epitopes SLYNTVATL and TVYYGVPVWK from HIV+ control patients were used as positive controls.
- The study explored why vaccinees were non-responsive – non-response was not due to inherent defects or differences in the ability of these individuals to process and present antigen.

**HXB2 Location** gp160 (37–46)  
**Author Location** gp120 (37–46 LAI)  
**Epitope** TVYYGVPVWK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Keywords** review, escape  
**References** Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical sibling hemophiliac brothers were both infected with the same batch of factor VIII.
- One had a response to this epitope, the other did not. They were tested 6–8 years after infection.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

**HXB2 Location** gp160 (37–46)  
**Author Location** gp120 (36–45)  
**Epitope** TVYYGVPVWK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** gp160 (37–46)  
**Author Location** gp120 (37–46)  
**Epitope** TVYYGVPVWK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Keywords** rate of progression, acute/early infection  
**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)

- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

**HXB2 Location** gp160 (37–46)  
**Author Location**  
**Epitope** TVYYGVPVWK  
**Epitope name** Env-VK9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A03, 0/20 (0%) recognized this epitope.

**HXB2 Location** gp160 (37–46)  
**Author Location** gp160 (37–46)  
**Epitope** TVYYGVPVWK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, escape  
**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** gp160 (37–46)  
**Author Location** gp120  
**Epitope** TVYYGVPVWK  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (A3)  
**Donor MHC** A01, A03, B39, B44, Cw4, Cw6  
**Assay type** T-cell Elispot  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Missale *et al.* 2004

- HIV-specific T-cell response was tested in patients exposed to blood from a patient with highly replicating HIV; these patients were nosocomially infected with HBV, but uninfected with HIV. HIV-specific T-cell responses were directed to structural and non-structural HIV proteins in 2 patients, suggesting that the virus replicated in these patients sufficiently to prime a cell-mediated immune response that protected them from HIV infection.

- This patient responded to 3/11 HIV epitopes tested in an IFN $\gamma$  EliSpot assay. Responses were detected 16 and 20 weeks after exposure, but were lost by week 80.

**HXB2 Location** gp160 (37–46)

**Author Location** gp120

**Epitope** TVYYGVPVWK

**Epitope name** A3-TK11(gp120)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (37–46)

**Author Location** Env (49–58)

**Epitope** TVYYGVPVWK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** gp160 (37–46)

**Author Location** Env (37–46)

**Epitope** TVYYGVPVMK

**Immunogen** peptide-HLA interaction

**Species (MHC)** (A11, A3, A68)

**Assay type** HLA binding

**Keywords** binding affinity, immunodominance

**References** Racape *et al.* 2006

- Interaction between purified HLA-A3 molecules and several dominant CD8 epitopes was characterized. Amplitude, stability, and kinetic parameters of the interaction between HLA-A3, peptides, and anti-HLA mAbs were tested.
- Epitopes tested bound strongly to HLA-A3 and formed very stable complexes.
- Gag epitope RLRPGGKKK and Nef epitope RLAFFHHVAR complexes with HLA-A3 were not recognized by the A11.1 mAb specific to HLA-A3 alleles. The proposed explanation was that Arg at position P1 of the peptide may push the  $\alpha$ 2 helix residue and affect mAb recognition.

**HXB2 Location** gp160 (37–53)

**Author Location** (C consensus)

**Epitope** TVYYGVPVWKEAKTTLF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3201)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** gp160 (37–53)

**Author Location** (C consensus)

**Epitope** TVYYGVPVWKEAKTTLF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*4301)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** gp160 (37–53)

**Author Location** (C consensus)

**Epitope** TVYYGVPVWKEAKTTLF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

- HXB2 Location** gp160 (37–53)  
**Author Location** Env  
**Epitope** TVYYGVPVWKEATTTLF  
**Epitope name** ENV-06  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, immunodominance  
**References** Zhao *et al.* 2007
- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
  - 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
  - Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
  - 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
  - This peptide, TVYYGVPVWKEA $\dagger$ TTTLF differs from the consensus C sequence TVYYGVPVWKEAkTTTLF at 1 amino acid position, i.e. by 5.9%.

- HXB2 Location** gp160 (37–53)  
**Author Location** gp120  
**Epitope** TVYYGVPVWKEATTTLF  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004
- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3

- frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
  - In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
  - This immunodominant, frequently targeted overlapping peptide, TVYYGVPVWKEATTTLF, had an overall frequency of recognition of 22.7% - 25.4% AA, 19.2% C, 18.2% H, 28.6% WI. This peptide is included in a 41 aa gp120 highly reactive region to be used for vaccine design.

- HXB2 Location** gp160 (38–48)  
**Author Location** gp120 (45–55)  
**Epitope** VYYGVPVWKEA  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw7)  
**References** Nehete *et al.* 1998a
- Three long-term non-progressors and one asymptomatic HIV+ individual were studied and found to have HLA class I C-restricted CD8+ Env-specific CTLs – Cw7 specific CTL were found against three peptides, including this one.
  - HLA-C antigens are expressed on lymphoid cells to a lesser extent than either HLA-A or -B.
  - HLA-C confers protection against lysis by natural killer cells and by non-MHC-restricted effector T cells and Cw7 directly governs this resistance to lysis – the authors hypothesize that pathogens that inhibit antigen expression and class I expression may particularly down regulate Cw7, thus triggering non-MHC restricted killing.

- HXB2 Location** gp160 (38–48)  
**Author Location** gp120 (38–48)  
**Epitope** VYYGVPVWKEA  
**Immunogen**  
**Species (MHC)** (Cw7)  
**Keywords** subtype comparisons, viral fitness and reversion  
**References** de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
  - Present in 46/51 Brazilian HIV sequences.

- HXB2 Location** gp160 (38–52)  
**Author Location**  
**Epitope** VYYGVPVWKEATTTL  
**Subtype** B  
**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade *HIV component:* gp140

**Species (MHC)** mouse

**Assay type** proliferation, T-cell Elispot

**References** Kumar *et al.* 2006b

- A recombinant plasmid DNA construct expressing env gp140 from B clade isolate 6101 was developed.
- The construct was highly immunogenic in mice and cross-reacted with clade C peptides. 3 immunodominant peptides were mapped out. Proliferation was observed in CD4+, CD8+ and CCR+ memory T cells.
- Immunodominant peptide VYYGVPVWKEATTTL overlapped with the SYFPEITHI database predicted epitope YGVVWKEA for the Balb/C mouse H2-Kd loci.

**HXB2 Location** gp160 (42–51)

**Author Location** gp120 (42–51 PV22)

**Epitope** VPVWKEATTT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5501 epitope.

**HXB2 Location** gp160 (42–51)

**Author Location** gp120 (42–51)

**Epitope** VPVWKEATTT

**Immunogen**

**Species (MHC)** (B\*5501, B55)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 32/51 Brazilian HIV sequences; variant VPVWKEAKTT present in all Brazilian subtype C sequences.

**HXB2 Location** gp160 (42–51)

**Author Location** gp120 (42–51 PV22)

**Epitope** VPVWKEATTT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B55)

**References** Brander & Walker 1995

- P. Johnson, unpublished.

**HXB2 Location** gp160 (42–51)

**Author Location** gp120 (41–55)

**Epitope** VPVWKEATTT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B55)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** gp160 (42–52)

**Author Location** gp120 (42–52)

**Epitope** VPVWKEATTTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*3501 epitope.

**HXB2 Location** gp160 (42–52)

**Author Location** gp120 (42–52)

**Epitope** VPVWKEATTTL

**Immunogen**

**Species (MHC)** (B\*3501)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 32/51 Brazilian HIV sequences; variant VPVWKEAKTTL present in all Brazilian subtype C sequences.
- This epitope is associated with the rapid-progression HLA, B35; epitope has low variation in non-C subtypes, but high variability in BF recombinants suggests that CTL may be exerting selective pressure on BF viruses.

**HXB2 Location** gp160 (42–52)

**Author Location** (C consensus)

**Epitope** VPVWKEAKTTL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5301)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** gp160 (42–52)

**Author Location** (C consensus)

**Epitope** VPVWKEAKTTL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5301)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- VPVWKEAKTTTL is an optimal epitope.

**HXB2 Location** gp160 (42–52)  
**Author Location** gp120 (42–52 PV22)  
**Epitope** VPVWKEATTTTL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Keywords** subtype comparisons  
**References** Cao *et al.* 1997a

- VPVWKEATTTTL is the consensus sequence for clades B and D.
- VPVWKDAETTL is the consensus sequence for clade A and it is cross-reactive.
- VPVWKEADTTTL is the consensus sequence for clade C and it is cross-reactive.
- VPVWKEADTTTL is the consensus sequence for clade E and even with three substitutions still retains some cross-reactivity.

**HXB2 Location** gp160 (42–52)  
**Author Location** gp120 (41–51)  
**Epitope** VPVWKEATTTTL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** gp160 (42–52)  
**Author Location** Env (41–50)  
**Epitope** VPVWKEATTTTL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 4/9 patients recognized this epitope.

**HXB2 Location** gp160 (42–52)  
**Author Location** gp120  
**Epitope** VPVWKEATTTTL  
**Epitope name** B35-VL11(gp120)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (42–52)

**Author Location**  
**Epitope** VPVWKEATTTTL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope VPVWKEATTTTL elicited a magnitude of response of 310 SFC with a functional avidity of 0.1nM and binding affinity of 10730nM.

**HXB2 Location** gp160 (42–52)  
**Author Location** Env (43–52 BH10, LAI)  
**Epitope** VPVWKEATTTTL

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this peptide is PVWKEATTTTL) has similarity with the platelet membrane glycoprotein IIIA precursor (GLIIIA) (integrin beta-3) (CD61); PLYKEATSTF.

**HXB2 Location** gp160 (42–61)  
**Author Location** gp120 (49–68)  
**Epitope** VPVWKEATTTTLFCASDAKAY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** gp160 (42–61)

**Author Location** gp120 (49–68 SF2)

**Epitope** VPVWKEATTTLFCASDAKAY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- Three of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A2, A3, B8, B62; HLA-A3, A24, B7, B38.

**HXB2 Location** gp160 (42–61)

**Author Location** gp120 (49–68 SF2)

**Epitope** VPVWKEATTTLFCASDAKAY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** gp160 (42–61)

**Author Location** gp120 (11–30)

**Epitope** VPVWKEATTTLFCASDAKAY

**Epitope name** VPV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, escape

**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0–80% as efficiently as the index peptide, and the relative efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive peptides found not to vary over time. It was one of four epitopes that were not precisely defined.

**HXB2 Location** gp160 (50–59)

**Author Location** gp120 (50–59)

**Epitope** TTLFCASDAK

**Immunogen**

**Species (MHC)** (A3)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 46/51 Brazilian HIV sequences.

**HXB2 Location** gp160 (50–59)

**Author Location** Env (62–71)

**Epitope** TTLFCASDAK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** gp160 (51–59)

**Author Location** gp160 (51–59)

**Epitope** TLFCASDAK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, TLFCASDAK, was predicted to be restricted by HLA A\*0301, A\*1101, A\*3101, A\*3301, A\*6601 and A\*6801.

**HXB2 Location** gp160 (51–59)  
**Author Location** gp120 (51–59)  
**Epitope** TLFCASDAK  
**Immunogen**  
**Species (MHC)** (A3)  
**Keywords** subtype comparisons, viral fitness and reversion  
**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 47/51 Brazilian HIV sequences.

**HXB2 Location** gp160 (51–59)  
**Author Location** Env (63–71)  
**Epitope** TLFCASDAK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3 supertype)  
**Keywords** supertype, rate of progression  
**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** gp160 (52–61)  
**Author Location** gp120 (59–68 HXB2)  
**Epitope** LFCASDAKAY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2402)  
**References** Lieberman *et al.* 1992

- CTL epitope defined by T cell line and peptide mapping.
- C. Brander notes that this is an A\*2402 epitope in the 1999 database.

**HXB2 Location** gp160 (52–61)  
**Author Location** gp120 (53–62 LAI)  
**Epitope** LFCASDAKAY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2402)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*2402 epitope.

**HXB2 Location** gp160 (52–61)  
**Author Location** gp120 (53–62)  
**Epitope** LFCASDAKAY  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (A24)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** gp160 (52–61)  
**Author Location** gp120 (53–62)  
**Epitope** LFCASDAKAY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A24)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , T-cell Elispot, CD8 T-cell Elispot granzyme B  
**Keywords** characterizing CD8+ T cells  
**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Two of seven patients responded to this peptide with GzB producing cells, and a different patient with IFN-gamma producing cells.

**HXB2 Location** gp160 (52–61)  
**Author Location** gp120  
**Epitope** LFCASDAKAY  
**Epitope name** A24-LY10(gp120)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A24)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (52–61)  
**Author Location**  
**Epitope** LFCASDAKAY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A24)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope LFCASDAKAY elicited a magnitude of response of 240 SFC with a functional avidity of 5nM.

**HXB2 Location** gp160 (52–61)

**Author Location** gp120 (53–62 LAI)

**Epitope** LFCASCAKAY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B38)

**References** Shankar *et al.* 1996

- Uncertain whether optimal, binds A24 as well.

**HXB2 Location** gp160 (52–71)

**Author Location** gp120 (59–78)

**Epitope** LFCASDAKAYDTEVHINVWAT

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** gp160 (52–71)

**Author Location** gp120 (59–78 SF2)

**Epitope** LFCASDAKAYDTEVHINVWAT

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2 and B-21.

**HXB2 Location** gp160 (59–69)

**Author Location** (C consensus)

**Epitope** KAYETEVHNVW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- KAYETEVHNVW is an optimal epitope.

**HXB2 Location** gp160 (59–69)

**Author Location**

**Epitope** KAYETEVHNVW

**Epitope name** KW11

**Immunogen**

**Species (MHC)** human (B58)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B58 epitope.

**HXB2 Location** gp160 (61–69)

**Author Location**

**Epitope** YETEVHNVW

**Epitope name** YW9

**Immunogen**

**Species (MHC)** human (B\*1801)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1801 epitope.

**HXB2 Location** gp160 (61–69)

**Author Location** gp120 (61–69 HIV-MN)

**Epitope** YETEVHNVW

**Epitope name** YW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1801)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Positions 2 and 5 in the epitope had potentially experienced positive selection. YgTEVHNVW, YdTEVHNVW, YETeAHNVW and YdTEeAHNVW escape variants were found.

**HXB2 Location** gp160 (62–80)

**Author Location** gp120 (69–88 SF2)

**Epitope** DTEVHNVWATHACVPTDPN

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a



- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2 and B-21.

**HXB2 Location** gp160 (64–73)  
**Author Location** Env (63–72 SF2)  
**Epitope** EVHNVWATHA  
**Subtype** A, B, C, CRF01\_AE, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2603)  
**Country** Japan  
**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay, HLA binding  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction, rate of progression, escape, variant cross-recognition or cross-neutralization

**References** Kawashima *et al.* 2005

- A\*26 is associated with slow progression to disease and is common in Asian populations (about 20%). 31/110 HIV peptides that carried the A\*2603 motif ([VTILP] at P2, [ML] at the C-terminus) bound to HLA-A\*2603. Only 2 of these were epitopes and could induce specific CD8 T-cell responses in PBMC from HLA-A\*2603 positive subjects.
- This epitope induced specific CD8+ T cells in chronically infected individuals with A\*2603, but not A\*2601.
- 5 common B clade variants were synthesized. EVHNVWATHA and EVHNiWATHA bound to A\*2603 with equal affinity. EiHNVWATHA and EaHNVWATHA bound to A\*2603 with reduced affinity. EmHNVWATHA and EkHNVWATHA could not bind to A\*2603. A CTL clone that recognized EVHNVWATHA was able kill cells prepulsed with the 3 peptide variants that could bind to A\*2602.
- EVHNVWATHA is the most common form in clades A, B, C, and E (CRF01), but EaHNiWATHA is the most common form in clade D.

**HXB2 Location** gp160 (67–75)  
**Author Location** Env (67–)  
**Epitope** NIWATHACV  
**Epitope name** Env67(2I)  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* peptide *HIV component:* gp120 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction  
**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31

novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.

- This peptide was a good A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 1/17 HIV+ HLA-A2 subjects.
- The variant nVwathacv was also immunogenic in transgenic mice, but was not recognized in the 17 people tested.

**HXB2 Location** gp160 (73–81)  
**Author Location** gp41 (73–81)  
**Epitope** ACVPTDPNP  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*2902, B\*1402  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** HAART, ART, escape, viral fitness and reversion  
**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, ACVPTDPNP, was found to be 0.023/day, with SE of 0.016.
- Five mutations at the fifth position of Env gp41 73-81 were all shown to confer limited CTL escape.

**HXB2 Location** gp160 (75–84)  
**Author Location** gp120  
**Epitope** VPTDPNPPEV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding  
**References** Höhn *et al.* 2003

- The M. tuberculosis HLA-A2 restricted epitope VLT-DGNPPEV and this HLA-A2 HIV-1 gp120 VPTDPNPPEV epitope are cross-recognized. HLA-A2+ patients with pulmonary tuberculosis exhibit cross-reactivity with the HIV gp160 epitope, and those with HIV-1 infection have cross-reactive responses to M.tuberculosis antigen.

**HXB2 Location** gp160 (78–86)  
**Author Location** gp120 (77–85)  
**Epitope** DPNPQEVVL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)

**References** Ogg *et al.* 1998b

- This epitope was included to illustrate the specificity of HIV-tetrameric staining, in a cross-sectional study correlating HLA A\*0201 CTL effector cells and low viral load.

**HXB2 Location** gp160 (78–86)**Author Location** gp120 (77–85 SF2)**Epitope** DPNPQEVVL**Immunogen** HIV-1 infection**Species (MHC)** human (B\*3501)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*3501 epitope.

**HXB2 Location** gp160 (78–86)**Author Location** gp120 (77–85 SF2)**Epitope** DPNPQEVVL**Immunogen** HIV-1 infection**Species (MHC)** human (B\*3501)**References** Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- 2/7 B35-positive individuals have a CTL response to this epitope.
- This epitope is highly variable.
- The substitutions: 1N, 3S and 7I, 7L and 9M, 8I, 8K all abrogate specific CTL lysis, while only 8K reduces binding to B\*3501.
- The substitution 8V to 8E does not reduce specific CTL activity.

**HXB2 Location** gp160 (78–86)**Author Location** Env (77–85)**Epitope** DPNPQEVVL**Immunogen** HIV-1 infection**Species (MHC)** human (B\*3501)**Keywords** HAART, ART**References** Ogg *et al.* 1999

- CTL effector levels were measured after potent ARV therapy using HLA-tetramer complexes for the A\*0201 epitopes SYLVANTVATL and ILKEPVHGV in seven patients, and the B\*3501 epitope DPNPQEVVL in one additional patient.
- Levels of CTL effectors typically decline for 5-7 days and then rebound, fluctuating during the first two weeks of therapy.
- After the early fluctuation, there was a steady exponential decay with a median half-life of 45 days.

**HXB2 Location** gp160 (78–86)**Author Location** Env (77–85)**Epitope** DPNPQEVVL**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**References** Dyer *et al.* 1999

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

**HXB2 Location** gp160 (78–86)**Author Location****Epitope** DPNPQEVVL**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Keywords** acute/early infection**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and a close temporal relationship between the number of circulating HIV-specific T cells and viral load.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWIILGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** gp160 (78–86)**Author Location** (SF2)**Epitope** DPNPQEVVL**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Keywords** rate of progression**References** Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation.

**HXB2 Location** gp160 (78–86)**Author Location** gp120 (77–85 SF2)**Epitope** DPNPQEVVL**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Keywords** HAART, ART, acute/early infection**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.

- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 0/1 group 3.

**HXB2 Location** gp160 (78–86)

**Author Location**

**Epitope** DPNPQEVVL

**Epitope name** Env-DL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 3/20 (15%) recognized this epitope.

**HXB2 Location** gp160 (78–86)

**Author Location** gp120 (78–86)

**Epitope** DPNPQEVVL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** A3, A33, B14, B35, Cw\*0401, Cw\*0802

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** gp160 (78–86)

**Author Location** (C consensus)

**Epitope** DPNPQEMVL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** gp160 (78–86)

**Author Location** gp120 (47–55)

**Epitope** DPNPQEVAL

**Epitope name** DPN

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, escape

**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This epitope was one of six epitopes found to be under positive selection for escape mutations, and was mostly replaced by an escape variant between days 66 and 369 (dpnpqeAal) and then replaced by a new escape variant (dpnpqevPl) by day 635.

**HXB2 Location** gp160 (78–86)

**Author Location** gp120

**Epitope** DPNPQEVVL

**Epitope name** B35-DL9(gp120)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (78–86)**Author Location** gp120 (77–85 SF2)**Epitope** DPNPQEVVL**Immunogen** HIV-1 infection**Species (MHC)** human (B35, B51)**References** Shiga *et al.* 1996

- Binds HLA-B\*3501 and B\*5101 – binds and kills gp120-vaccinia virus infected cells carrying B35 or B51.

**HXB2 Location** gp160 (78–86)**Author Location** gp120 (77–85)**Epitope** DPNPQEVVL**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human (B51)**Keywords** HIV exposed persistently seronegative (HEPS)**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** gp160 (78–86)**Author Location** gp160 (78–86)**Epitope** DPNPQEVVL**Immunogen** HIV-1 infection**Species (MHC)** human (B51)**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8**Country** Netherlands**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** rate of progression, escape**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.

- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** gp160 (88–96)**Author Location** gp120 (88–96 HIV-MN)**Epitope** NVTENFMW**Epitope name** NW9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2501)**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape, immune evasion, optimal epitope**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Positions 5 and 7 in the epitope had potentially experienced positive selection. NVT-EdFdmW, NVTEeFdmW and NVTEsFdmW escape variants were found.

**HXB2 Location** gp160 (89–97)**Author Location** gp160**Epitope** VTEEFNMWK**Subtype** A, B, C, D**Immunogen** HIV-1 infection, vaccine*Vector/Type:* vaccinia *Strain:* A clade, B

clade, D clade NDK, C clade consensus

*HIV component:* Env**Species (MHC)** human**Donor MHC** A\*3201, A\*3601, B\*5301, B\*8101, Cw\*0401, Cw\*0804; A\*2402, A\*3201, B\*5101, B\*5301, Cw\*0401, Cw\*0602**Country** Kenya**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization**References** McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.

- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. VTEEFNMWK responses were detected in 2 women who had Env responses to all 4 clades, and clade A gave the highest responses; a VnEEFNMWK variant was in clade B and D, and the clade C Env carried VnEEFNWWe. One woman also reacted with RAIEAQQHL, the other with KNCSFNMTT.
- Both women that reacted with VTEEFNMWK carried HLA-B\*5301, the only common HLA allele.

**HXB2 Location** gp160 (89–98)  
**Author Location** Env  
**Epitope** VTENFNMWKN  
**Epitope name** 1284  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11, A68 supertype)  
**Donor MHC** A01, A68, B15, B40, Cw03; A03, A11, B14, B51, Cw08, Cw13  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, supertype, computational epitope prediction, cross-presentation by different HLA  
**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for VTENFNMWKN:17%. This epitope can be presented by the A11, A68 supertype.

**HXB2 Location** gp160 (90–104)  
**Author Location**  
**Epitope** TENFNMWKNMVEQM  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN  
*HIV component:* Gag-Pol, gp120, gp41  
**Species (MHC)** human  
**Donor MHC** A\*2501, A\*3002; B\*0702, B\*1801  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes  
**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.

- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** gp160 (103–111)  
**Author Location** Env (102–110)  
**Epitope** QMHEDIISL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** binding affinity, TCR usage  
**References** Kmiecik *et al.* 1998a

- CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL – all have A2 anchor residues.
- The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*.
- Peptides 4.3 and D1 bound HLA-A\*0201 molecules with high affinity.
- Peptides 4.3 and D1 stimulated CTL with a relatively limited TCR V $\beta$  repertoire.

**HXB2 Location** gp160 (104–112)  
**Author Location** gp160 (104–112)  
**Epitope** MHEDIISLW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** gp160 (104–112)  
**Author Location** gp120 (104–112)  
**Epitope** MHEDIISLW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3801)  
**Donor MHC** A26, A3, B\*3801, B7, Cw\*0702, Cw\*1203  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** binding affinity, acute/early infection, early-expressed proteins  
**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** gp160 (104–112)

**Author Location**

**Epitope** MHEDIISLW

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A3, A32; B38, B64

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85–86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was recognized by a placebo patient after infection.

**HXB2 Location** gp160 (104–112)

**Author Location**

**Epitope** MHEDIISLW

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A1, A2; B38, B8

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85–86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** gp160 (104–119)

**Author Location** gp120 (111–126 IIIB)

**Epitope** MQEDIISLWDQSLKPC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Macatonia *et al.* 1991

- Primary CTL response with cells from non-infected donors stimulated by the peptide.

**HXB2 Location** gp160 (105–117)

**Author Location** gp120 (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Clerici *et al.* 1991a

- Helper and cytotoxic T cells can be stimulated by this peptide (T2)

**HXB2 Location** gp160 (105–117)

**Author Location** gp120 (MN)

**Epitope** HEDIISLWDQSLK

**Immunogen** HIV-1 infection

**Species (MHC)** chimpanzee

**References** Lubeck *et al.* 1997

- No epitope-specific CTL were detected in chimpanzees immunized with adenovirus-HIV-1 MN gp160 recombinant despite a response to peptides P18 and T1.
- Helper and cytotoxic T cells have been found to be stimulated by this peptide (T2)

**HXB2 Location** gp160 (105–117)

**Author Location** gp120 (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human

**References** Pinto *et al.* 1995

- CTL and T helper cell reactivity in healthcare workers exposed to HIV.

**HXB2 Location** gp160 (108–116)

**Author Location** Env (107–115 subtype B)

**Epitope** IISLWDQSL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade MN *HIV component:* gp160

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity

**References** Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

**HXB2 Location** gp160 (108–116)

**Author Location** gp120 (108–116)

**Epitope** IISLWDQSL

**Immunogen**

**Species (MHC)** (A2.1)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 46/51 Brazilian HIV sequences.

**HXB2 Location** gp160 (109–117)

**Author Location** Env (109–117 CM243 subtype CRF01)

**Epitope** ISLWDQSLK

**Epitope name** E109-117

**Subtype** CRF01\_AE

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Bond *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in the HEPS study subject 265 who was HLA A2/A11, and had been predicted to be a possible A11 epitope using Epimer in Bond *et al.* [2001]

**HXB2 Location** gp160 (109–117)

**Author Location** gp120 (109–117)

**Epitope** ISLWDQSLK

**Immunogen**

**Species (MHC)** (A11)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 48/51 Brazilian HIV sequences.

**HXB2 Location** gp160 (110–118)

**Author Location** gp120 (110–118)

**Epitope** SLWDQSLKP

**Immunogen**

**Species (MHC)** (A03)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 48/51 Brazilian HIV sequences.

**HXB2 Location** gp160 (110–118)

**Author Location** Env

**Epitope** SLWDQSLKP

**Epitope name** 1328

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A02, A03, B08, B51, Cw01, Cw07

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction, immunodominance

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for SLWDQSLKP: 50%. Immunodominant epitope.

**HXB2 Location** gp160 (112–130)

**Author Location** gp120 (119–139 SF2)

**Epitope** WDQSLKPCVKLTPLCVSLK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2 and B-21.

**HXB2 Location** gp160 (112–131)

**Author Location** gp120 (MN)

**Epitope** WDQSLKPCVKLTPLCVTLNC

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** assay standardization/improvement, HAART, ART

**References** Chitnis *et al.* 2003

- 17 perinatally HIV-1 infected children (0.08-16 years) were evaluated for HLA-A2-restricted IFN-gamma CD8+ CTL responses against 4 immunodominant peptides that carry HLA-A2 epitopes. Two peptides were from gp120 (one at position 112, one from the V3 loop), and one each was from gp41 and Gag. 15/17 patients responded to the Gag peptide, 13/17 to the gp41 and the non-V3 gp120 peptides, and 11/17 responded to the V3 loop. 4 children recognized all 4 peptides.

**HXB2 Location** gp160 (117–126)

**Author Location** Env (72–81)

**Epitope** KPCVKLTPLC

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Jin *et al.* 2000b

- This B7 epitope is one of three subdominant CTL responses detected in a long-term non-progressor.
- A dominant B7 epitope was defined using conventional methods, and three additional sub-dominant HLA B7 epitopes were defined by first using a non-anchor based strategy, EpiMatrix, to identify 2078 possible epitopes in the autologous HIV-1, followed by B7 anchor residue prediction to narrow the set to 55 peptides for experimental testing.

**HXB2 Location** gp160 (117–126)**Author Location** Env**Epitope** KPCVKLTPLC**Epitope name** 1295**Subtype** multiple**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Country** United States**Assay type** T-cell Elispot**Keywords** binding affinity, computational epitope prediction**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KPCVKLTPLC: 27%. This epitope was previously reported but not confirmed in this study.

**HXB2 Location** gp160 (117–126)**Author Location** gp120 (117–126)**Epitope** KPCVKLTPLC**Immunogen****Species (MHC)** (B7)**Keywords** subtype comparisons, viral fitness and reversion**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 47/51 Brazilian HIV sequences.

**HXB2 Location** gp160 (121–129)**Author Location** Env (121–129)**Epitope** KLTPLCVTL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*02)**Country** United States**Assay type** Intracellular cytokine staining, Other**Keywords** rate of progression, escape, immune evasion**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- One patient developed a response to epitope KLTPLCVTL after primary infection at early chronic infection. This was one of the epitopes targeted by broad HLA-A2-restricted CTL responses.

**HXB2 Location** gp160 (121–129)**Author Location** Env**Epitope** KLTPLCVTL**Immunogen** vaccine*Vector/Type:* DNA**Species (MHC)** transgenic mouse (A\*0201)**References** Ishioka *et al.* 1999

- A minigene vaccine construct encoding 6 HLA 2.1 and 3 HLA A11 restricted CTL epitopes, the universal Th cell epitope PADRE (pan-DR epitope) and an ER translocating signal sequence was constructed.
- The epitopes were chosen for dominant recognition by CTLs during HBV and HIV infections in humans.
- HLA transgenic mice were used for quantitating *in vivo* immunogenicity of DNA vaccines encoding HLA-restricted CTL epitopes – strong responses were observed to all nine epitopes, and CTL memory persisted up to four months after a single injection.

**HXB2 Location** gp160 (121–129)**Author Location** Env (120–128 subtype B)**Epitope** KLTPLCVTL**Subtype** B**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade MN*HIV component:* gp160**Species (MHC)** human (A\*0201)**Keywords** binding affinity**References** Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.



- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

**HXB2 Location** gp160 (121–129)

**Author Location** Env (120–128)

**Epitope** KLTPLCVTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity, TCR usage

**References** Kmiecik *et al.* 1998a

- CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL—all have A2 anchor residues.
- The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*.
- Peptides 4.3 and D1 bound HLA-A\*0201 molecules with high affinity.
- Peptides 4.3 and D1 stimulated CTL with a relatively limited TCR V $\beta$  repertoire.
- In a longitudinal study, the CTL response to the variable D2 epitope diminished over time, while the response to the conserved epitope D1 stayed higher over time.

**HXB2 Location** gp160 (121–129)

**Author Location** Env (134–)

**Epitope** KLTPLCVTL

**Epitope name** Env-134

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity, subtype comparisons, super-type, computational epitope prediction

**References** Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- 2/22 individuals with chronic HIV-1 infection recognized this epitope in ELISPOT.
- 0/12 acutely infected individuals recognized this epitope.
- KLTPLCVTL binds to four HLA-A2 supertype alleles: A\*0201, A\*0202, A\*0203 and A\*6802 (highest affinity).

**HXB2 Location** gp160 (121–129)

**Author Location** Env

**Epitope** KLTPLCVTL

**Epitope name** Env 134

**Immunogen** vaccine, *in vitro* stimulation or selection, computer prediction

*Vector/Type:* DNA

**Species (MHC)** human, humanized mouse (A\*0201)

**Assay type** Cytokine production, T-cell Elispot

**Keywords** subtype comparisons, computational epitope prediction, escape, TCR usage, variant cross-recognition or cross-neutralization

**References** McKinney *et al.* 2004

- This study examined variant recognition of epitopes presented by A\*0201 and A\*1101. Numerous amino acid substitutions can be introduced into epitopes without disrupting their recognition by CTLs, although epitopes with multiple substitutions were less recognized. An algorithm was constructed for prediction of epitopes capable of inducing responses to a great number of variant epitopes.
- A total of 19 variant forms of Env 134 were identified of which 10 were recognized by CTLs from transgenic mice immunized with the parental form.
- Env 134 epitope was present in 80% of HIV sequences of diverse M group HIV-1 subtypes.

**HXB2 Location** gp160 (121–129)

**Author Location** Env

**Epitope** KLTPLCVTL

**Epitope name** K9L

**Immunogen** vaccine

*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140 $\Delta$ V3

**Species (MHC)** transgenic mouse (A\*0201)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells

**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** gp160 (121–129)

**Author Location** Env

**Epitope** KLTPLCVSL

**Epitope name** P10L

**Immunogen** vaccine

*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140 $\Delta$ V3

**Species (MHC)** transgenic mouse (A\*0201)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells

**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** gp160 (121–129)

**Author Location**

**Epitope** KLTPLCVTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A02)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KLTPLCVTL elicited a magnitude of response of 530 SFC with a functional avidity of 0.1nM.

**HXB2 Location** gp160 (121–129)

**Author Location** gp120 (120–128 LAI)

**Epitope** KLTPLCVTL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160

**Species (MHC)** human (A2)

**References** Dupuis *et al.* 1995

- CTL from HLA-A2 positive subject react with this peptide.

**HXB2 Location** gp160 (121–129)

**Author Location** gp120 (120–128)

**Epitope** KLTPLCVTL

**Immunogen** vaccine

*Vector/Type:* vaccinia

**Species (MHC)** human (A2)

**References** Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D<sup>d</sup> – this transgene is the only MHC molecule expressed in the mice.

- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.

- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWYCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFD-SRL)

- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.

- KLTPLCVTL was recognized by 3 of the patients.

**HXB2 Location** gp160 (121–129)

**Author Location** gp120 (120–128)

**Epitope** KLTPLCVTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** dendritic cells

**References** Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.
- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.
- KLTPLCVTL is a conserved HLA-A2 epitope included in this study – all six patients had this sequence as their HIV direct sequence, and a detectable CTL response.
- CTL demonstrated against peptide-coated target, epitope is naturally processed and enhancible with vaccine.

**HXB2 Location** gp160 (121–129)

**Author Location** gp120 (120–128)

**Epitope** KLTPLCVTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Kmiecik *et al.* 1998b

- Increased CTL response to cells expressing a VV construct  $\Delta$ v3 mutant compared with a full-length env gene product.

**HXB2 Location** gp160 (121–129)

**Author Location** gp120 (121–129)

**Epitope** KLTPLCVSL

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A2)

**Keywords** dendritic cells

**References** Zarling *et al.* 1999

- This study compares the ability of macrophages and dendritic cells to stimulate primary responses in CD8+ lymphocytes isolated from HLA-appropriate HIV-uninfected donors using peptide-pulsed APC – the dendritic cells performed better as APC for the stimulation of primary responses.
- Strong CTL responses were elicited by the epitopes DRFYK-TLRA and GEIYKRWII when presented by either immature or mature dendritic cells – macrophages were not able to prime a CTL response against DRFYKTLRA.
- A weak response to KLTPLCVSL was stimulated using macrophages as the APC.
- No detectable response was observed for the following previously-defined HIV epitopes: KIRLRPGGK, ILKEPVHGV, IRLRPGGK, GPKVKQWPL.

**HXB2 Location** gp160 (121–129)

**Author Location** gp120 (120–128)

**Epitope** KLTPLCVTL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** gp160 (121–129)

**Author Location** gp120 (121–129 IIIB)

**Epitope** KLTPLCVTL

**Epitope name** D1

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, DNA with protein boost  
*Strain:* B clade IIIB *HIV component:*  
gp160, gp160ΔV3 *Adjuvant:* IL-12

**Species (MHC)** mouse (A2)

**Keywords** vaccine-specific epitope characteristics

**References** Kiszka *et al.* 2002

- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with a full length gp160 or with gp160deltaV3, with the V3 loop deleted. Mice given gp160deltaV3 had a broader immune response than those given gp160, with increased responses to conserved HLA-A2 epitopes in the C1 region of gp120, KLTPLCVTL, and the C-term region of gp41, SLLNATAIAV.
- Greater resistance was conferred by the gp160deltaV3 than the gp160 vaccine to a challenge of vaccinia expressing heterologous gp160 from primary isolates (VI-06 and 89.6), and the resistance was conferred by CD8+ T-cells.

**HXB2 Location** gp160 (121–129)

**Author Location** Env (121–)

**Epitope** KLTPLCVTL

**Epitope name** Env121

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- 3/17 HIV-infected HLA-A2+ people recognized this epitope.

**HXB2 Location** gp160 (121–129)

**Author Location** gp160 (121–129)

**Epitope** KLTPLCVTL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding

**Keywords** acute/early infection, optimal epitope

**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was recognized both during acute and chronic infection, but more often during chronic infection.

**HXB2 Location** gp160 (121–129)

**Author Location** Env (121–129 HXB2)

**Epitope** KLTPLCVTL

**Epitope name** D1

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* multiple epitope immunogen *HIV component:* p17/p24 Gag, Pol *Adjuvant:* IL-12

**Species (MHC)** transgenic mouse (A2)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-specific epitope characteristics, vaccine antigen design

**References** Bolesta *et al.* 2005

- Immunization of transgenic mice with a codon-optimized hGagp17p24-Polp51 DNA plasmid, consisting of clusters of highly conserved CTL epitopes presented by multiple MHC class I alleles, induced 2- to 5-fold higher CD8+ T-cell responses than the corresponding full-length proteins. The modified proteins had the ribosomal frameshift deleted, as well as the potentially immunosuppressive p15, and protease and integrase. This correlated with higher protection against challenge with Gag and Pol expressing recombinant vaccinia virus. Mice immunized with the hGagp17p24-Polp51 also showed an elevated level of type 1 cytokine production as well as an increased titer of p24- and RT-specific IgG2 antibody responses.
- Four A2 gag/pol epitopes were tested, and this Env A2 epitope was used as a negative control.

**HXB2 Location** gp160 (121–129)

**Author Location** gp160**Epitope** KLTPLCVTL**Epitope name** A2-KL9(gp160)**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (121–129)**Author Location** Env (134–142)**Epitope** KLTPLCVTL**Immunogen** HIV-1 infection**Species (MHC)** human (A2 supertype)**Keywords** supertype, rate of progression**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind four of the five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

**HXB2 Location** gp160 (155–163)**Author Location** gp160**Epitope** KNCSFNMTT**Subtype** A, B, C, D**Immunogen** HIV-1 infection, vaccine*Vector/Type:* vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus  
*HIV component:* Env**Species (MHC)** human**Donor MHC** A\*2402, A\*3201, B\*5101, B\*5301, Cw\*0401, Cw\*1604**Country** Kenya**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization**References** McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. VTEEFNMWK responses were detected in 2 women who had Env responses to all 4 clades, and clade A gave the highest responses; a VnEEFNMWK variant was in clade B and D, and the clade C Env carried VnEEFNMWK. One woman also reacted with RAIEAQQHL, the other one with KNCSFNMTT. KNCSFNMTT was identical in clades A and C, while clade B carried KNCSFNMis, clade D carried KNISFNMTT.

**HXB2 Location** gp160 (156–165)**Author Location** gp120 (156–165)**Epitope** NCSFNISTSI**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*08)**Keywords** epitope processing**References** Ferris *et al.* 1999

- Recognized by CTL clone LWF A5, isolated from a lab worker exposed to HIV-1 in 1985.
- The processing of this epitope is TAP1/2-dependent, as are most Env epitopes, and it contains two N-linked glycosylation sites that are glycosylated in Env.
- Only peptide that has been deglycosylated, a process that changes asparagine (N) to aspartic acid (D) was recognized: the aspartic acid at position 5 was critical, position 1 could be either D or N.
- This peptide also contains a Cys involved in a disulfide linkage but reducing conditions did not effect recognition by CTL clone LWF A5.
- The HIV-1 Env epitopes are typically processed by a TAP1/2 dependent mechanism, which involves cotranslational translocation into the ER, glycosylation, export back into the cytosol, and deglycosylation for processing, and retransport into the ER for the association with class I molecules.
- The particular pathway of generating an epitope may have an impact on the presentation of that epitope, quantitatively as well as qualitatively.

**HXB2 Location** gp160 (156–165)**Author Location** gp120 (156–165 IIIB)**Epitope** NCSFNISTSI**Immunogen** HIV-1 infection**Species (MHC)** human (Cw8)**References** Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- NCSFNITTSI, a variant found in HIV-1 MN, was not recognized, thus this epitope was type-specific.
- NCSFNISTSI contains two potential N-linked glycosylation sites and cysteine residue, possibly related to the requirement for a high sensitizing dose of peptide for CTL activity.

**HXB2 Location** gp160 (156–165)  
**Author Location** Env (162–171 BH10, LAI)  
**Epitope** NCSFNISTSI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Maksutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is STSIRGKVQK) has similarity with the macrophage colony stimulating factor I receptor fragment SISIRLKVQK.

**HXB2 Location** gp160 (188–207)  
**Author Location** gp120 (193–212 BRU)  
**Epitope** TTSYTLTSCNTSVITQACPK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Dadaglio *et al.* 1991

• Defined through blocking CTL activity, and Env deletions.

**HXB2 Location** gp160 (190–208)  
**Author Location** gp41 (190–208)  
**Epitope** SYKLTSCNTSVITQACPKV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A3, A32, B15, B51  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** HAART, ART, escape, viral fitness and reversion  
**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, SYKLTSCNTSVITQACPKV, was found to be 0.005/day, with SE of 0.001.

- In the subject studied, the monotonic outgrowth of a Q199K mutation in Env gp41 was observed over a period of 1,028 days.

**HXB2 Location** gp160 (191–200)  
**Author Location** gp120 (194–202 CM243 subtype CRF01)  
**Epitope** YRLINCNTSV  
**Epitope name** E191-200  
**Subtype** CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2.

**HXB2 Location** gp160 (191–200)  
**Author Location** gp120 (194–202 CM243 subtype CRF01)  
**Epitope** YRLINCNTSV  
**Subtype** CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** subtype comparisons  
**References** Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by four amino acids, KLTSCNTSV.
- This epitope was somewhat conserved in 4/8 subtypes: CRF01 (E), B, C, and D.

**HXB2 Location** gp160 (191–208)  
**Author Location** gp120  
**Epitope** YRLISCNTSVITQACPKV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but

the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.

- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J. Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, YRLISCNTSVITQACPKV, had an overall frequency of recognition of 15.3% - 11.9% AA, 23.1% C, 18.2% H, 9.5% WI.

**HXB2 Location** gp160 (192–200)

**Author Location** gp120 (192–199)

**Epitope** KLTSCNTSV

**Epitope name** SL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Keywords** HAART, ART

**References** Rinaldo *et al.* 2000

- Administration of triple-drug antiretroviral therapy (IDV, 3TC and ZDV) sometimes showed a transient increase and other times failed to increase CTL responses in patients with advanced HIV disease, but there is a stable population of tetramer stained HIV-specific CD8+ CD45RO+ cells that persist after therapy and long periods of virus being below the level of detection.

**HXB2 Location** gp160 (192–200)

**Author Location** Env (192–200)

**Epitope** RLISCNTSV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol.

Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

**HXB2 Location** gp160 (192–200)

**Author Location** gp120 (199–207)

**Epitope** TLTSCNTSV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Brander *et al.* 1996

- This epitope was recognized by PBMC from 6/14 HIV+ asymptomatic patients.
- This epitope was used along with pol CTL epitope ALQDS-GLEV and a tetanus toxin T helper epitope for a synthetic vaccine.
- This vaccine failed to induce a CTL response, although a helper response was evident.

**HXB2 Location** gp160 (192–200)

**Author Location** gp120 (192–199 HXB2R)

**Epitope** KLTSCNTSV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Brander *et al.* 1995

- Epitope predicted on HLA binding motif, and studied in the context of inclusion in a synthetic vaccine.

**HXB2 Location** gp160 (192–200)

**Author Location** gp120 (192–199)

**Epitope** KLTSCNTSV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART

**References** Huang *et al.* 2000

- The single cell ELISPOT assay was optimized and highly specific, and found to work well even after the primary cells had been frozen and thawed.
- Increases in gamma interferon producing cells were observed in response to anti-retroviral therapy using single cell IFN-gamma-production ELISPOT.

**HXB2 Location** gp160 (192–200)

**Author Location** gp120 (197–205)

**Epitope** TLTSCNTSV

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (A2)

**References** Garboczi *et al.* 1992

- Crystallization of HLA-A2 molecules complexed with antigenic peptides – refers to Dadaglio *et al.* 1991.

**HXB2 Location** gp160 (192–200)

**Author Location** gp120 (161–169)

**Epitope** ILRSCNTSV

**Epitope name** ILR

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, escape  
**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0-80% as efficiently as the index peptide, and the relatively efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive epitopes found not to vary over time.

**HXB2 Location** gp160 (192–211)  
**Author Location** gp120 (199–219 SF2)  
**Epitope** SLTSCNTSVITQACPKVSFE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2, -B21.

**HXB2 Location** gp160 (196–210)  
**Author Location** Env  
**Epitope** CNTSTITQACPKVSF  
**Epitope name** Peptide37  
**Subtype** B, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human, mouse  
**Country** United States  
**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, epitope processing, optimal epitope  
**References** Zhan *et al.* 2007

- By studying 4 subjects and surveying the database, it was found that for Env protein, some CTL epitopes cluster in similar "hotspots" as CD4 T-cell epitopes. This is not subtype-specific and shows that regions rather than specific peptides are targeted by T cells.
- Peptide37, CNTSTITQACPKVSF, was targeted by CTLs of one HIV-1 positive subject.

**HXB2 Location** gp160 (199–207)  
**Author Location** gp160 (202–210)  
**Epitope** SVITQACPK

**Subtype B**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*11)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This putative epitope, SVITQACPK, was detected and confirmed within overlapping peptide YRLISC-NTSVITQACPKV.

**HXB2 Location** gp160 (199–207)  
**Author Location** Env (202–210)  
**Epitope** SVITQACPK  
**Subtype B**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*1101)  
**Keywords** subtype comparisons, TCR usage  
**References** Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A\*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A\*1101 epitopes was recognized in a clade specific manner. Two other HLA A\*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- SVITQACPK was found to elicit clade-specific responses in clade B (SVITQACPK is most common, sAitqacpk is most common variant in clade A, C and D) and clade E (saiKqacpk is most common). SVITQACPK was recognized by CTL from 3/5 B clade infected Japanese subjects, and aiKqacpk by CTL from 0/7 E clade infected Thai subjects, so this seems to be a B clade exclusive epitope.
- The binding of the three variant peptides to HLA A\*1101 was comparable, implicating TCR interaction differences.

**HXB2 Location** gp160 (199–207)  
**Author Location** gp160 (199–207)  
**Epitope** SVITQACPK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*1101)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** gp160 (201–215)  
**Author Location** Env

**Epitope** ITQACPKVSFEPIPI**Subtype** A, B, C, D**Immunogen** vaccine*Vector/Type:* DNA prime with vaccinia boost, protein *Strain:* B clade 1007, B clade 1035 *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse**Country** United States**Assay type** Cytokine production**Keywords** subtype comparisons, immunodominance**References** Brown *et al.* 2006

- A vaccine study with B clade Envs in mice was undertaken to assess a subtype-specificity of responses. Four T-cell hybridomas responsive to subtype B envelope proteins were tested against 20 different subtype B envelope proteins and a protein each from subtypes A, C and D. IL-2 production was measured.
- No consistent correlation was found between T cell specificity towards epitopes from a certain (B) subtype or lack of specificity towards other (A, C, D) subtype.
- Not only did T-cell specificity not vary with subtype, but pairwise sequence comparisons of HIV gp120 envelope sequences showed that some US-derived sequences were more similar to sequences from distant countries than to each other.
- Changes in core epitopes, flanking and distant regions, all affected responsiveness of the hybridomas to different subtype Env epitopes, showing that it is not only core changes that can eliminate T cell reactivity to an epitope.
- The above findings were substantiated by database analyses showing that epitope distributions are not necessarily dictated by subtype.
- This paper lists several variants of the epitope above, ITQACPKVSFEPIPI.

**HXB2 Location** gp160 (201–225)**Author Location** gp120 (201–225 LAI)**Epitope** ITQACPKVSFEPIPIHYCAPAGFAI**Subtype** B**Immunogen** vaccine*Vector/Type:* vaccinia *HIV component:* gp160**Species (MHC)** human (CD4+ CTL)**References** Johnson *et al.* 1994b; Johnson *et al.* 1994a

- CD4+ CTL isolated from LAI IIIB gp160 vaccinees.

**HXB2 Location** gp160 (202–221)**Author Location** gp120 (209–228)**Epitope** TQACPKVSFEPIPIHYCAPA**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** gp160 (202–221)**Author Location** gp120**Epitope** TQACPKVSFEPIPIHYCAPA**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** TCR usage**References** Weekes *et al.* 1999b

- Peptide 740.18: Almost all CD8+ T cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed the CD28 depleted cell population.
- HIV CTL responses to 3 Env and 2 Gag peptides were studied.
- The clonal composition of the TCR V $\beta$  responses were studied and was found to be highly focused, with one TCR beta-chain sequence tending to dominate the peptide-specific response – clones to this epitope were V $\beta$ 13.1.

**HXB2 Location** gp160 (202–221)**Author Location** gp120**Epitope** TQACPKVSFEPIPIHYCAPA**Immunogen** HIV-1 infection**Species (MHC)** human**References** Weekes *et al.* 1999a

- Peptide 740.18: Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28- CD8+ CTLp populations.

**HXB2 Location** gp160 (202–221)**Author Location** gp120 (209–228 SF2)**Epitope** TQACPKVSFEPIPIHYCAPA**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.

**HXB2 Location** gp160 (202–221)**Author Location** gp120 (209–228 SF2)**Epitope** TQACPKVSFEPIPIHYCAPA**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** gp160 (202–221)**Author Location** gp120 (173–192)**Epitope** TQACPKVSFEPIPIHYCAPA**Epitope name** Peptide 740.18**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A11, A29, B44, B8**Country** United Kingdom**Assay type** Flow cytometric T-cell cytokine assay, Other**Keywords** HAART, ART, immunodominance, TCR usage, memory cells**References** Weekes *et al.* 2006



- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintenance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

**HXB2 Location** gp160 (205–219)

**Author Location**

**Epitope** CPKVSFPEIPIHYCA

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade *HIV component:* gp140

**Species (MHC)** mouse

**Assay type** proliferation, T-cell Elispot

**References** Kumar *et al.* 2006b

- A recombinant plasmid DNA construct expressing env gp140 from B clade isolate 6101 was developed.
- The construct was highly immunogenic in mice and cross-reacted with clade C peptides. 3 immunodominant peptides were mapped out. Proliferation was observed in CD4+, CD8+ and CCR+ memory T cells.
- Immunodominant peptide CPKVSFPEIPIHYCA overlapped with the SYFPEITHI database predicted epitope CPKMSFEPI for the Balb/C mouse H2-Kd loci.

**HXB2 Location** gp160 (206–220)

**Author Location** Env

**Epitope** PKVSFPEIPIHYCAP

**Subtype** A, B, C, D

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost, protein *Strain:* B clade 1007, B clade 1035

**Species (MHC)** mouse

**Assay type** Cytokine production

**Keywords** subtype comparisons, immunodominance

**References** Brown *et al.* 2006

- A vaccine study with B clade Envs in mice was undertaken to assess a subtype-specificity of responses. Four T-cell hybridomas responsive to subtype B envelope proteins were tested against 20 different subtype B envelope proteins and a protein each from subtypes A, C and D. IL-2 production was measured.
- No consistent correlation was found between T cell specificity towards epitopes from a certain (B) subtype or lack of specificity towards other (A, C, D) subtype.
- Not only did T-cell specificity not vary with subtype, but pairwise sequence comparisons of gp120 envelope sequences showed that some US-derived sequences were more similar to sequences from distant countries than to each other.

- Changes in core epitopes, flanking and distant regions, all affected responsiveness of the hybridomas to different subtype Env epitopes, showing that it is not only core changes that can eliminate T cell reactivity to an epitope.
- The above findings were substantiated by database analyses showing that epitope distributions are not necessarily dictated by subtype.
- This paper lists several variants of the epitope above, PKVS-FEPIPIHYCAP.

**HXB2 Location** gp160 (206–220)

**Author Location** Env

**Epitope** PKVSFPEIPIHYCAP

**Epitope name** Peptide39

**Subtype** B, D

**Immunogen** HIV-1 infection

**Species (MHC)** human, mouse

**Country** United States

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, epitope processing, optimal epitope

**References** Zhan *et al.* 2007

- By studying 4 subjects and surveying the database, it was found that for Env protein, some CTL epitopes cluster in similar "hotspots" as CD4 T-cell epitopes. This is not subtype-specific and shows that regions rather than specific peptides are targeted by T cells.
- Peptide39, PKVSFPEIPIHYCAP, was targeted by CTLs of one HIV-1 positive subject.

**HXB2 Location** gp160 (207–216)

**Author Location** gp120 (subtype A)

**Epitope** KMTFPEIPIH

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human (A29)

**Keywords** subtype comparisons

**References** Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.
- CTL derived from subtype A clade infection (patient SP 528), recognized the subtype A version of the peptide (KMS-FEPIPIH), had a slightly reduced specific lysis using the B clade version of the peptide (KVSFPEIPIH), and no lysis using the D clade version of the epitope (KVTFPEIPIH)
- Patient SP 528 is HLA A1, A29, B57, B81, Bw4, Bw6.

**HXB2 Location** gp160 (207–224)

**Author Location** (C consensus)

**Epitope** KVSFDPIPIHYCAPAGYA

**Subtype C****Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0401)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** gp160 (208–216)**Author Location** Env**Epitope** VSFPEIPIH**Epitope name** 1329**Subtype** multiple**Immunogen** HIV-1 infection**Species (MHC)** human (A3)**Donor MHC** A03, A23, B49, B57; A03, A24, B27, B57, Cw13, Cw18**Country** United States**Assay type** T-cell Elispot**Keywords** binding affinity, computational epitope prediction**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for VSFPEIPIH: 58%

**HXB2 Location** gp160 (208–217)**Author Location** gp120 (subtype B)**Epitope** VSFPEIPIHY**Subtype** B**Immunogen** HIV-1 exposed seronegative**Species (MHC)** human (A29)**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNT-VATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** gp160 (208–217)**Author Location** gp120 (263–272)**Epitope** VSFPEIPIHY**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human (A29)**Keywords** HIV exposed persistently seronegative (HEPS)**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** gp160 (208–217)**Author Location** gp120**Epitope** VSFPEIPIHY**Immunogen** HIV-1 infection**Species (MHC)** human (A29)**Assay type** Intracellular cytokine staining**Keywords** immunodominance, genital and mucosal immunity**References** Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T cells responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 1/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

**HXB2 Location** gp160 (208–219)**Author Location** Env**Epitope** VSFPEIPPHYCA**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Keywords** epitope processing**References** Cao *et al.* 2002

- SP 511 is an A2 restricted CTL clone generated from a Ugandan subject that recognizes VSFPEIPPHYCA.
- CTL could be activated by a fusion protein of an HIV protein and anthrax lethal factor (LFn-HIV) that promotes antigen presenting cell uptake of exogenous protein and allows processing through the MHC class I pathway. This strategy for CTL detection could allow antigen presentation without generation of cells by the standard methods of using live viral vectors carrying a protein, or by loading the cells with peptides and by-passing processing.

**HXB2 Location** gp160 (208–219)**Author Location** Env**Epitope** VSFPEIPPHYCA**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Donor MHC** A\*0202, A\*0301, B\*0702, B\*1516**Country** United States**Keywords** escape, acute/early infection**References** Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of

early nonsynonymous mutations were observed within previously reported CTL epitopes.

- K to E mutation was observed in position 4.

**HXB2 Location** gp160 (209–217)

**Author Location** (C consensus)

**Epitope** SFDPIPIHY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*29)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the S1 residue of SFDPIPIHY are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** gp160 (209–217)

**Author Location** (LAI)

**Epitope** SFPEPIPIHY

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*2902)

**Keywords** optimal epitope

**References** Altfeld 2000; Frahm *et al.* 2008

**HXB2 Location** gp160 (209–217)

**Author Location** gp160 (207–215 BORI, WEAU)

**Epitope** SFPEPIPIHY

**Epitope name** gp160 SY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2902)

**Donor MHC** A\*2902, B\*1402, Cw\*0802; A\*2902, B\*0801, B\*4403

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined, WEAU and BORI, had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape. This epitope was recognized in both patients.

- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified. The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.

- Four escape variants to the SFPEPIPIHY epitope were found in the patient BORI. SFdPIPIHY came up first, at day 55 from onset of symptoms, and caused a reduced cytotoxic response. By day 218, two rare forms were found, SIEPIPIHf and SiEPIPIHf. By day 556, only tFEPIPIHY was found. The weakest response was detected in the double mutant, SiEPIPIHf, yet tFEPIPIHY was the form that persisted.
- In WEAU, a minor variant, SsEPIPIHY was present at day 41. The SIEPIPIHf variant first came up day 136, gave a reduced CTL response, and then came to be the dominant form. Other variants were SFPEPIInY and SFPEPIIdf.

**HXB2 Location** gp160 (209–217)

**Author Location** gp120 (213–221 SF2)

**Epitope** SFPEPIPIHY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A29)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A29+ individuals that had a CTL response to this epitope broken down by group: 1/3 group 1, 0/0 group 2, and 0/0 group 3.

**HXB2 Location** gp160 (209–217)

**Author Location** gp120 (209–217)

**Epitope** SFPEPIPIHY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A29)

**Donor MHC** 1261: A\*0201, A29, B58, B62, Cw\*0304, Cw\*1601; 1168: A\*0201, A29, B44, B60, Cw16, Cw3

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- Two subjects recognized this epitope during primary infection, both in the context of A29.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** gp160 (209–217)

**Author Location** (C consensus)

**Epitope** SFDPIPIHY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A29)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** gp160 (209–217)

**Author Location** (B consensus)

**Epitope** SFPEIPIHY

**Epitope name** SY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A29)

**Donor MHC** A28, A29, B14, B44, Cw8

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope

**HXB2 Location** gp160 (209–217)

**Author Location** gp160 (209–217)

**Epitope** SFPEIPIHY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*2902, B\*1402; A\*2902, B\*0801, B\*4403

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimates of escape rate for this epitope, SFPEIPIHY, were found to be 0.072 and 0.041/day (optimistic escape rate = 0.13), with SEs of 0.041 and 0.005 respectively, in 2 subjects.
- In the first subject, rapid loss of wild type at this epitope (primarily due to a E211D mutation) was observed. In the second subject, a Y217F mutation grew out over time.

**HXB2 Location** gp160 (209–217)

**Author Location** Env

**Epitope** SFPEIPIHY

**Subtype** B, D

**Immunogen** HIV-1 infection

**Species (MHC)** human, mouse

**Country** United States

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, epitope processing, optimal epitope

**References** Zhan *et al.* 2007

- By studying 4 subjects and surveying the database, it was found that for Env protein, some CTL epitopes cluster in similar "hotspots" as CD4 T-cell epitopes. This is not subtype-specific and shows that regions rather than specific peptides are targeted by T cells.
- SFPEPIHY was targeted by the human subject with a positive IFN- $\gamma$  response to Peptide39, PKVSFPEPIHY-CAP. This epitope is shifted by one residue compared to the immunodominant murine CD4 T-cell epitope, FEPIPIHYC.

**HXB2 Location** gp160 (212–226)

**Author Location**

**Epitope** PIPHYCAPAGFAIL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** gp160 (212–231)

**Author Location** gp120

**Epitope** PIPHYCAPAGFAILKCNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** TCR usage

**References** Weekes *et al.* 1999b

- Peptide 740.19: Almost all CD8+ T cells are CD28+ at birth, and the proportion of CD28-CD8+ cells increases with age – this study examines the contribution of CD8+CD28- cells to CTL memory pools for CTL clones specific for two persistent human viruses, CMV and HIV – clones were found to be similarly distributed in the CD28 depleted cell population.
- HIV CTL responses to 3 Env and 2 Gag peptides were studied.
- The clonal composition of the TCR V $\beta$  responses was studied and was found to be highly focused, with one TCR beta-chain sequence tending to dominate the peptide-specific response – clones to this epitope were V $\beta$ 13.6.

**HXB2 Location** gp160 (212–231)

**Author Location** gp120 (183–202)

**Epitope** PIPHYCAPAGFAILKCNK

**Epitope name** Peptide 740.19

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A2, A24, B27, B62

**Country** United Kingdom

**Assay type** Flow cytometric T-cell cytokine assay, Other  
**Keywords** HAART, ART, immunodominance, TCR usage, memory cells

**References** Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintenance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

**HXB2 Location** gp160 (212–231)

**Author Location** gp120

**Epitope** PIPHYCAPAGFAILKCNK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Jin *et al.* 1998b

- Progressive HIV-1 infection and CD4 decline was associated decreased the IL-2-expandable HIV-1 CTL response in 10 asymptomatic HIV-infected patients – this observation may be partially due to a reduction and impaired function of T helper cells, CTL exhaustion and APC dysfunction.
- Continued presence of HIV-1 specific memory cells (CTLp) was observed in three patients, one to GIWGC SGKLICTTAV, one to ALIWEDLRSLCLFSY, and one to PIPHYCAPAG-FAILKCNK.

**HXB2 Location** gp160 (212–231)

**Author Location** gp120

**Epitope** PIPHYCAPAGFAILKCNK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Weekes *et al.* 1999a

- Peptide 740.19: Memory CTL specific for HIV-1 may contribute to oligoclonal expansions within the CD57+ CD28- CD8+ CTLp populations.

**HXB2 Location** gp160 (212–231)

**Author Location** gp120 (219–238 HXB2)

**Epitope** PIPHYCAPAGFAILKCNK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1992

- CTL epitope defined by T cell line and peptide mapping.

**HXB2 Location** gp160 (212–231)

**Author Location** gp120 (219–238)

**Epitope** PIPHYCAPAGFAILKCNK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** gp160 (217–226)**Author Location** gp120 (217–226 HIV-MN)**Epitope** YCAPAGFAIL**Epitope name** YL10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0102)**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape, immune evasion, optimal epitope**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Last position (10) in the epitope had potentially experienced positive selection. YCAPAGFAIi escape variant was found.

**HXB2 Location** gp160 (218–228)**Author Location** Env (218–228)**Epitope** CTPAGYAILKC**Subtype** CRF01\_AE**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201, A\*0206, A\*0207)**Country** Thailand**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** optimal epitope**References** Kantakamalakul *et al.* 2006

- T cell responses in CRF01\_AE infected individuals from Thailand were studied.
- Based on two overlapping peptide sequences that were both reactive, as well as conserved anchor residues, this peptide is suggested to contain an epitope.

**HXB2 Location** gp160 (237–246)**Author Location** Env**Epitope** GPCKNVSTVQ**Immunogen****Species (MHC)** human (B56)**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFN $\gamma$  production in an ELISPOT assay.

- GPCKNVSTVQ was newly defined as an epitope in this study, was shown to stimulate an ELISPOT response, and to bind to HLA-B7.

**HXB2 Location** gp160 (239–247)**Author Location** Env**Epitope** CTNVSTVQC**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-Cw8 restricted epitope, CTNVSTVQC was mutated to CqNVSTVQC in the daughter D2 isolate.

**HXB2 Location** gp160 (239–247)**Author Location** gp160 (237–245 BORI)**Epitope** CKNVSTVQC**Epitope name** gp160 CC9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0802)**Donor MHC** A\*2902, B\*1402, Cw\*0802**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** dynamics, immunodominance, escape, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three

patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.

- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- Four variants of the CKNVSTVQC epitope were found in the patient BORI. CeNVSTVQC and cCeNVSTVhC came up first, at day 6 from onset of symptoms. The CeNVSTVQC form was the form that persisted, with a second rare variant present at day 35, CgNVSTVQC. These variants were not tested for their impact on escape.

**HXB2 Location** gp160 (239–247)  
**Author Location** gp120 (241–249 LAI)  
**Epitope** CTNVSTVQC  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw8)  
**References** Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- CTNVSTVQC contains a potential N-linked glycosylation site and cysteine residues, possibly related to a requirement for a high sensitizing dose of peptide for CTL activity.

**HXB2 Location** gp160 (242–261)  
**Author Location** gp120 (249–268)  
**Epitope** VSTVQCTHGIRPVVSTQLLL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** gp160 (242–261)  
**Author Location** gp120 (249–268 SF2)  
**Epitope** VSTVQCTHGIRPVVSTQLLL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-2, -B21.

**HXB2 Location** gp160 (242–261)  
**Author Location** gp120 (249–268)  
**Epitope** VSTVQCTHGIRPVVSTQLLL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** gp160 (252–260)  
**Author Location** gp120 (255–263 SF2)  
**Epitope** RPIVSTQLL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**References** Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- Only 1/7 B35-positive individuals had a CTL response to this epitope.
- An I to V substitution at position 3 reduces specific lysis, but not binding to B\*3501.
- A Q to H substitution at position 7 abrogates specific lysis, but not binding to B\*3501.

**HXB2 Location** gp160 (252–260)  
**Author Location** gp120 (255–263 SF2)  
**Epitope** RPIVSTQLL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**References** Shiga *et al.* 1996

- Binds HLA-B\*3501.

**HXB2 Location** gp160 (252–260)  
**Author Location** (SF2)  
**Epitope** RPIVSTQLL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Keywords** rate of progression  
**References** Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation.

**HXB2 Location** gp160 (252–261)  
**Author Location** gp120 (252–261)  
**Epitope** KPVVSTQLLL  
**Immunogen**  
**Species (MHC)** (B07, B08)  
**Keywords** subtype comparisons, viral fitness and reversion  
**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 36/59 Brazilian HIV sequences; a common variant is rPVVSTQLLL found in subtype B and BF sequences.

**HXB2 Location** gp160 (252–261)  
**Author Location** Env  
**Epitope** RPVVSTQLLL  
**Immunogen**  
**Species (MHC)** human (B7)  
**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 of the predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFN $\gamma$  production in an ELISPOT assay.
- RPVVSTQLLL was one of the 15, and had been previously identified as an HLA-B7 epitope, and was confirmed in this study.

**HXB2 Location** gp160 (252–261)

**Author Location** Env

**Epitope** KPVVSTQLLL

**Epitope name** 1298

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7, B8)

**Donor MHC** A01, A03, B07, B08, Cw03, Cw07; A29, A30, B08, B44, Cw07, Cw16

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for KPVVSTQLLL: 46% Promiscuous epitope binding to B08 and B07.

**HXB2 Location** gp160 (252–261)

**Author Location** Env

**Epitope** RPVVSTQLLL

**Epitope name** 1305

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7, B8)

**Donor MHC** A29, A30, B08, B44, Cw07, Cw16

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, supertype, computational epitope prediction, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for RPVVSTQLLL: 41%. Supertype epitope, published B07, responses by B08 subject.

**HXB2 Location** gp160 (252–271)

**Author Location** gp120 (256–275 LAI)

**Epitope** RPVVSTQLLLNGSLAEEVV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Shankar *et al.* 1996

**HXB2 Location** gp160 (252–271)

**Author Location** Env (256–268 BH10, LAI)

**Epitope** RPVVSTQLLLNGSLAEEVV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Maksutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is STQLLLNGSLAEE) has similarity with the lymphatic endothelium-specific hyaluronan receptor LYVE-1 fragment TTRLVQGSRAEE.

**HXB2 Location** gp160 (280–288)

**Author Location** Env

**Epitope** NAKTIIVHL

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0602)

**Country** Thailand

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** immunodominance, optimal epitope

**References** Kantakamalakul *et al.* 2006

- T cell responses in CRF01\_AE infected individuals from Thailand were studied.
- Fine mapping of the peptide NAKTIIVHL, revealed a novel Cw\*0602-restricted epitope.

**HXB2 Location** gp160 (281–288)

**Author Location** (C consensus)

**Epitope** AKTIIVHL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0602)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the L8 residue of AKTIIVHL are associated with the presence of the HLA presenting molecule in the host.
- AKTIIVHL not optimized.

**HXB2 Location** gp160 (291–307)

**Author Location** gp120 (295–312 BRU)

**Epitope** SVEINCTRPNNTRKSI

**Immunogen** HIV-1 infection



**Species (MHC)** human (A2)

**References** Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

**HXB2 Location** gp160 (291–307)

**Author Location** gp120 (291–307 IIIB)

**Epitope** SVEINCTRPNNNTRKRI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, DNA with protein boost

*Strain:* B clade IIIB *HIV component:*

gp160 *Adjuvant:* IL-12

**Species (MHC)** mouse (A2)

**Keywords** vaccine-specific epitope characteristics

**References** Kiszka *et al.* 2002

- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with a full length gp160 or with gp160deltaV3, with the V3 loop deleted. Mice given gp160deltaV3 had a broader immune response than those given gp160, with increased responses to conserved HLA-A2 epitopes in the C1 region of gp120, KLTPLCVTL, and the C-term region of gp41, SLLNATAIAV.
- Greater resistance was conferred by the gp160deltaV3 than the gp160 vaccine to a challenge of vaccinia expressing heterologous gp160 from primary isolates (VI-06 and 89.6), and the resistance was conferred by CD8+ T-cells.
- The most intense CTL responses to the intact gp160 vaccine were directed at three V3 peptides.

**HXB2 Location** gp160 (291–307)

**Author Location** Env (292–301 BH10, LAI)

**Epitope** SVEINCTRPNNNTRKSI

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is VEINCTRPNN) has similarity with the FasI receptor precursor (Apoptosis-mediating surface antigen fas) (APO-1 antigen) (CD95 antigen) fragment VEINCTRQN.

**HXB2 Location** gp160 (296–305)

**Author Location** gp120 (296–305)

**Epitope** CTRPNNNTRK

**Immunogen**

**Species (MHC)** (A02, A03)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 283/515 Brazilian HIV sequences; a common variant is CTRPpNNTRK found in subtype B sequences.

**HXB2 Location** gp160 (296–305)

**Author Location** Env (296–305 B1 and B2)

**Epitope** CTRPNNNTRK

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A03, A32, B08, B62, Cw3)

**Country** Netherlands

**Assay type** Other

**Keywords** subtype comparisons, computational epitope prediction, superinfection

**References** Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01\_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-A03 restricted epitope, CTRPNNNTRK, varied to CTRPpNNTRK in B1 and B2, and CTRPpNNTRt in AE by the earliest time point taken, with no changes over time.

**HXB2 Location** gp160 (296–305)

**Author Location** Env

**Epitope** CTRPNNNTRK

**Epitope name** 1265

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2, A3)

**Donor MHC** A03, A23, B49, B57

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for CTRPNNNTRK: 51% Promiscuous epitope binding to A02 and A03.

**HXB2 Location** gp160 (297–322)

**Author Location** gp120 (297–322 IIIB)

**Epitope** TRPNNNTRKRIRIQRGPGRAFVTIGK

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

*HIV component:* V3 *Adjuvant:* liposome

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Chang *et al.* 1999

- Induction of peptide-specific CTLs in BALB/c mice was dependent on immunization with peptide encapsulated liposomes containing MPL as adjuvant.
- T26K (26mer) elicited a stronger AB and CTL response than R15K (a V3 15mer, RIQRGPGRAFVTIGK)

**HXB2 Location** gp160 (297–330)

**Author Location** Env (303–335 BX08)

**Epitope** TRPNNNTRKSIHIGPGRAFATGEIIGDIRQAH

**Immunogen** vaccine

*Vector/Type:* lipopeptide

**Species (MHC)** human

**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 6/10 reacted to this peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in five vaccinees.
- None of the 12 tested had an IgG response to gp120 or gp160 and vaccinees could be differentiated from HIV-1 seropositive individuals with a commercial HIV detection kit – no neutralizing antibodies were observed.

**HXB2 Location** gp160 (298–306)

**Author Location** gp120 (298–306)

**Epitope** RPNNNTRKS

**Epitope name** RS9

**Subtype** D

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07)

**Country** Kenya

**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement

**References** McKinnon *et al.* 2007

- The authors suggest that epitope variation has different effects on the HIV- specific immune responses of effector memory T cells (Tem) and central memory T cells (Tcm). They show a lack of correlation between IFN-gamma ELISPOT (Tem typical) and proliferation (Tcm typical) assays for specific epitopes in subjects. Since proliferating CTL also correlate with high intracellular IFN-gamma levels, they surmise that proliferating Tcm differentiate to express Tem functions.
- They also show that proliferating CTL numbers correlate with higher CD4 cell counts.
- Several patients responded strongly to epitope variants that were not part of their autologous HIV-1 sequences. Thus they suggest more comprehensive functional characterizations than the usual overnight IFN-gamma ELISPOTs as well as assessments of Tem versus Tcm specific responses rather than general CTL immune responses.
- 4 variants of this index epitope RPNNNTRKS, RS9, were tested in vitro - RPsNNTRKS, RPyNNTRKS, RPyNNTRqS, RPNNNTRrS. Autologous variants RPNNNTRrg and RPNNNTRtS were also detected. The rare variant RPyNNTRqS, found almost exclusively in clade B HIV (but absent in all subjects in this study), showed both proliferative as well as ELIspot responses. However, the intermediate RPyNNTRKS showed only a slight increase in proliferation but not in ELIspot detection.

**HXB2 Location** gp160 (298–307)

**Author Location** gp120 (298–307)

**Epitope** RPNNNTRKSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07)

**Keywords** epitope processing, TCR usage

**References** Ferris *et al.* 1999; Hammond *et al.* 1995

- The processing of this epitope is TAP1/2-dependent, as are most Env epitopes, and it contains an N-linked glycosylation site that is glycosylated in Env.
- Peptide that had been deglycosylated, a process that changes asparagine (N) to aspartic acid (D) (RPNDNTRKSI) was recognized a 100-fold more efficiently than either glycosylated or non-glycosylated RPNNNTRKSI.
- Position 5 is not involved with HLA B\*07 binding, so is probably important for TCR recognition.
- HIV-1 Env epitopes are typically processed by a TAP1/2 dependent mechanism, which involves cotranslational translocation into the ER, glycosylation, export back into the cytosol, and deglycosylation for processing, and retransport into the ER for the association with class I molecules.
- The particular pathway of generating an epitope may have an impact on the presentation of that epitope, quantitatively as well as qualitatively.

**HXB2 Location** gp160 (298–307)

**Author Location** gp120 (302–312 HXB2)

**Epitope** RPNNNTRKSI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0702 epitope.

**HXB2 Location** gp160 (298–307)

**Author Location** (C consensus)

**Epitope** RPNNNTRKSI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** gp160 (298–307)

**Author Location**

**Epitope** RPNNNTRKSI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B07)

- Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, immunodominance, optimal epitope  
**References** Bihl *et al.* 2006
- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
  - The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
  - EBV response patterns were not significantly altered by HIV coinfection.
  - Epitope RPNNNTRKSI elicited a magnitude of response of 1075 SFC with a functional avidity of 1nM and binding affinity of 23nM.
- HXB2 Location** gp160 (298–307)  
**Author Location** gp120 (302–312 HXB2)  
**Epitope** RPNNNTRKSI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**References** Safrit *et al.* 1994b
- CTL from two acute seroconversion cases.
- HXB2 Location** gp160 (298–307)  
**Author Location** gp120 (302–312 HXB2)  
**Epitope** RPNNNTRKSI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**References** Hammond *et al.* 1995
- Peptide processed by a TAP-1/2-dependent pathway only.
  - CTL from an acute seroconverter.
- HXB2 Location** gp160 (298–307)  
**Author Location** gp120 (302–312 HXB2)  
**Epitope** RPNNNTRKSI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**References** Wolinsky *et al.* 1996
- Longitudinal study of epitope variation *in vivo*.
- HXB2 Location** gp160 (298–307)  
**Author Location** gp120 (302–311 subtype B)  
**Epitope** RPNNNTRKSI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** subtype comparisons, immunodominance  
**References** Wilson *et al.* 1998b
- The extent of CTL interclade cross-reactivity from CTL isolated from individuals newly infected with B clade virus was studied, and extensive cross-reactivity was observed.
- Two HLA B7 individuals had CTL response to B\_LAI, A\_92UG037 and C\_92BR025 gp160, but were B clade strain MN non-responders – the authors note that the B7 epitope RPNNNTRKSI is immunodominant, conserved between the LAI and clade A and C strains, but is very divergent in MN (RPNYNKRKRI), and that this epitope might be dominating the specificity of the response in the HLA B7 individuals.
- HXB2 Location** gp160 (298–307)  
**Author Location** gp120 (303–312 SF2)  
**Epitope** RPNNNTRKSI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b
- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
  - The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
  - Previously described and newly defined optimal epitopes were tested for CTL response.
  - Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 1/3 group 2, and 1/1 group 3.
- HXB2 Location** gp160 (298–307)  
**Author Location** gp120 (298–307)  
**Epitope** RPNNNTRKSI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** rate of progression, acute/early infection  
**References** Day *et al.* 2001
- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
  - 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
  - Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
  - An acute seroconverter homozygous for the B7 allele recognized five B7-restricted epitopes.
  - The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
  - The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.
- HXB2 Location** gp160 (298–307)  
**Author Location** gp120 (298–307)  
**Epitope** RPNNNTRKSI

**Epitope name** B7-RI10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Donor MHC** A3, B7, Cw7**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 4/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 1/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** gp160 (298–307)**Author Location** gp120**Epitope** RPNNNTRKSI**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Donor MHC** A2, A3, B7, Bw6**Keywords** HAART, ART**References** Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful antiviral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

**HXB2 Location** gp160 (298–307)**Author Location** gp160 (298–307)**Epitope** RPNNNTRRGI**Epitope name** B7-RI10 Env**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** supervised treatment interruptions (STI), escape, early treatment, superinfection**References** Altfeld *et al.* 2002a

- An HIV+ individual given acute ARV and undergoing STI developed a strong CTL immune response, but despite this was shown to be superinfected with second B clade virus. Some epitope variants of the second infecting virus were resistant to the initial CTL response.

- The first infecting strain had the variant rpSnntrKSi, and the CTL response was higher to the second variant, RPNNNTR-RGI.

**HXB2 Location** gp160 (298–307)**Author Location** gp120**Epitope** RPNNNTRKSI**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Country** Netherlands**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** HIV exposed persistently seronegative (HEPS)**References** Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- No one pre-seroconversion, 0/9 HLA A2+ infection-resistant men, and 0/4 pre-seroconversion men who went on to become infected, reacted to this epitope.

**HXB2 Location** gp160 (298–307)**Author Location** Env (302–311)**Epitope** RPNNNTRKSI**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Country** Spain**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/7 patients recognized this epitope.

**HXB2 Location** gp160 (298–307)**Author Location** gp120 (303–312 IIIB)**Epitope** RPNNNTRKSI**Immunogen** HIV-1 infection**Species (MHC)** human (B7?)**Keywords** responses in children, mother-to-infant transmission**References** Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- RPNNNTRKDI and RPNNNTRKGI, naturally occurring variants, were found in non-transmitting mother – ability to recognize these variants has not yet been determined.

**HXB2 Location** gp160 (299–319)

**Author Location** Env (299–319)

**Epitope** PNNNTRKSIRIGPGQTFYA

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** gp160 (303–322)

**Author Location** gp120

**Epitope** TRKSIHIGPGRAFYTTE

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP)

*Strain:* B clade consensus *HIV component:*

Gag, V3

**Species (MHC)** mouse

**References** Luo *et al.* 1998

- Intramuscular injection of chimeric gag-env virus-like particles (VLPs) containing V3 loop sequences into BALB/c mice induce V3 specific CTL – TRKSIHIGPGRAFYTTE is a B subtype consensus that stimulated a cross-reactive CTL response.

**HXB2 Location** gp160 (304–318)

**Author Location** gp120 (304–318 IIIB)

**Epitope** RKSIRIQRGPGRFV

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP)

*Strain:* B clade IIIB, B clade MN, B

clade RF, B clade SF2, HIV-2 VLP *HIV*

*component:* Gag, V3

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Kang *et al.* 1999

- Virus-like particles could be formed from HIV-2 gag after deleting 143 amino acids at the C-terminal end – a proline rich region in positions 373–377 was critical to VLP formation.
- CTL responses in BALB/c mice were induced by chimeric gag-V3 particles against the V3 region of HIV-1 clade B isolates IIIB (SIRIQRGRAFVTI), MN (KRIHIGPGRFYTTK), RF (SITKGPGRVIYATGQ), and SF2 (SIYIGPGRFHTTGR)
- The vaccine induced CTL were cross-reactive with a broad spectrum of B clade isolates, with the exception of the RF V3 which did not induce CTL.

**HXB2 Location** gp160 (305–321)

**Author Location** gp120 (MN)

**Epitope** KRIHIGPGRFYTTK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** assay standardization/improvement, HAART, ART

**References** Chitnis *et al.* 2003

- 17 perinatally HIV-1 infected children (0.08–16 years) were evaluated for HLA-A2-restricted IFN- $\gamma$  CD8+ CTL responses against 4 immunodominant peptides that carry HLA-A2 epitopes. Two peptides were from gp120 (one at position 112, one from the V3 loop), and one each was from gp41 and Gag. 15/17 patients responded to the Gag peptide, 13/17 to the gp41 and the non-V3 gp120 peptides, and 11/17 responded to the V3 loop. 4 children recognized all 4 peptides.

**HXB2 Location** gp160 (306–322)

**Author Location** gp160 (LAI)

**Epitope** SIRIQGPGRAFVTIGI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI

*HIV component:* gp160 *Adjuvant:* alu-

minum hydroxide, CpG immunostimulatory

sequence (ISS)

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Keywords** immunodominance, Th1, Th2

**References** Deml *et al.* 1999

- Addition of CpG oligodeoxynucleotide to a gp160/alum vaccine given to BALB/c mice shifted the response to Th0/Th1 from Th2, but no still CTL response to this immunodominant epitope was induced.

**HXB2 Location** gp160 (307–324)

**Author Location** (C consensus)

**Epitope** IRIGPGQTFYATGDII

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*1801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** gp160 (308–321)

**Author Location** Env (IIIB)

**Epitope** RIQRGPGRFVTIG

**Epitope name** P18IIIB

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

*HIV component:* V3

**Species (MHC)** mouse (Dd)

**Keywords** binding affinity, Th1

**References** Ahlers *et al.* 2001

- BALB/c and A.AL were immunized with an Env-peptide vaccine construct containing the CTL epitope P18IIIB and the T helper epitope T1, KQIINMWQEVGKAMYA.

- Substitution of Glu (wt) to Ala in T1, kqiiimwqAvgkamya, caused increased affinity for MHC class II Ek, resulting in the upregulation of CD40L in the responding Th cells, and shifting the response towards Th1. Increased Th responses stimulated DCs to produce higher levels of IL-12, and B7-1 and B7-2, and enhanced CTL responses to P18.
- The modified epitope, T1A, elicited stronger protection against increasing doses of viral challenge with vaccinia expressing HIV-1 IIIB gp120 compared to the wt epitope T1.

**HXB2 Location** gp160 (308–321)

**Author Location** Env (gp160)

**Epitope** RIQRGPGRAFVTIK

**Epitope name** P18IIIB

**Immunogen** vaccine

*Vector/Type:* hemagglutinating virus of Japan (HVJ)-liposome *Strain:* B clade IIIB  
*HIV component:* gp160

**Species (MHC)** mouse

**Donor MHC** H-2d

**Assay type** Cytokine production, Chromium-release assay

**Keywords** genital and mucosal immunity

**References** Sakaue *et al.* 2003

- BALB/c mice were immunized nasally with HIVgp160-encapsulated hemagglutinating virus of Japan (HVJ)-liposome. Vaccination induced IgG in serum and IgA in nasal wash, saliva, fecal extract, and vaginal wash, with some ability to neutralize the primary field isolate HIV-MNp.
- Th1 and Th2-type responses were stimulated, as well as gp160 V3-specific MHC class I-restricted CTL responses.

**HXB2 Location** gp160 (308–322)

**Author Location** Env (315–329)

**Epitope** RIQRGPGRAFVTIGK

**Epitope name** P18

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* HIV-1

**Species (MHC)** mouse (A\*0201)

**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Singh *et al.* 2002; Sykes & Johnston 1999

- C3H (H-2k) transgenic mice carrying a fused HLA-A\*0201 alpha1 and alpha2 and H-2Dk alpha3 hybrid class I molecule were immunized using an epidermal gene gun with an ubiquitin expression library of 32 plasmids that spanned the HIV-1 genome. Ubiquitin targets the expressed HIV-1 peptides to the proteasome.
- A single immunization with the UB-HIV-1 library vaccine induced potent, stable and multivalent CTL responses against all library members.
- Immunodominant epitopes SLYNTVATL (Gag), ILKEPVHGV (Pol), RIQRGPGRAFVTIGK (Env) and AFHHVAREK (Nef) elicited strong CD8+/IFN- responses and stimulated CTL that were functional in a Cr-release assay and against wild type antigen.

- The presence of multiple plasmids HLA-A\*0201-restricted CTL epitopes did not decrease CTL immunogenicity, and CTL responses to single peptide immunizations were comparable to responses based on mixtures of either 16 or 32 peptides.

**HXB2 Location** gp160 (308–322)

**Author Location** Env (308–322 B1 and B2)

**Epitope** RIQRGPGRAFVTIGK

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A03, A32, B08, B62, Cw3)

**Country** Netherlands

**Assay type** Other

**Keywords** subtype comparisons, computational epitope prediction, superinfection

**References** Kozaczynska *et al.* 2007

- The influence of superinfection upon changes in HIV-1 strains was studied in a triple infected subject. While continuous expression of all three strains was observed, the LTR promoters of subtype AE had highest activity of all 3 strains, and subtype B2 had the lowest. Env-V3 sequences were present in higher numbers in strains B2 and CRF01\_AE. Recombination was seen between viruses B1/B2 in gag and vpr genes.
- This HLA-A03 restricted epitope, RIQRGPGRAFVTIGK, varied to slliaPGRAFyatGe in B1, sllhmGPGkAFFtGe in B2, and sllhmGPGqvFyrtGd in AE by the earliest time point taken, with no changes over time.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (315–329 IIIB)

**Epitope** RIQRGPGRAFVTIGK

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* gp160

**Species (MHC)** human (A11)

**References** Achour *et al.* 1994

- One of 3 HLA type restrictions associated with this peptide.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (315–329 BRU)

**Epitope** RIQRGPGRAFVTIGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (315–329 IIIB)

**Epitope** RIQRGPGRAFVTIGK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Clerici *et al.* 1991a

- Helper and cytotoxic T cells can be stimulated by this peptide (P18)

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (308–322 IIIB)

**Epitope** RIQRGPGRAFVTIGK

**Subtype** B

- Immunogen** vaccine  
*Vector/Type:* DNA, DNA with protein boost  
*Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* IL-12
- Species (MHC)** mouse (A2)
- Keywords** vaccine-specific epitope characteristics
- References** Kiszka *et al.* 2002
- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with a full length gp160 or with gp160deltaV3, with the V3 loop deleted. Mice given gp160deltaV3 had a broader immune response than those given gp160, with increased responses to conserved HLA-A2 epitopes in the C1 region of gp120, KLTPLCVTL, and the C-term region of gp41, SLLNATAIAV.
  - Greater resistance was conferred by the gp160deltaV3 than the gp160 vaccine to a challenge of vaccinia expressing heterologous gp160 from primary isolates (VI-06 and 89.6), and the resistance was conferred by CD8+ T-cells.
  - The most intense CTL responses to the intact gp160 vaccine were directed at three V3 peptides.
- HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (315–329 IIIB)  
**Epitope** RIQRGPGRAFVTIGK  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160
- Species (MHC)** human (A2, A3)  
**References** Achour *et al.* 1993
- Two of 3 HLA type restrictions associated with this peptide.
- HXB2 Location** gp160 (308–322)  
**Author Location** gp160 (308–322)  
**Epitope** RIQRGPGRAFVTIGK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, escape  
**References** Geels *et al.* 2003
- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
  - This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.
- HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (315–329 IIIB)  
**Epitope** RIQRGPGRAFVTIGK  
**Immunogen** vaccine
- Vector/Type:* peptide *Strain:* B clade IIIB  
*HIV component:* V3
- Species (MHC)** mouse (D<sup>d</sup>)  
**References** Takahashi *et al.* 1989a
- Positions R(8) and F(10) are important for MHC/peptide interaction.
- HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (315–329 IIIB)  
**Epitope** RIQRGPGRAFVTIGK  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade IIIB  
*HIV component:* V3
- Species (MHC)** mouse (D<sup>d</sup>)  
**References** Sastry *et al.* 1992
- Free peptide injected into the footpad of a mouse could stimulate specific CTL.
- HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (315–329 IIIB)  
**Epitope** RIQRGPGRAFVTIGK  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade MN  
*HIV component:* V3
- Species (MHC)** mouse (D<sup>d</sup>)  
**References** Ahlers *et al.* 1997b
- PCLUS 3-18MN synthetic peptide vaccine construct contained T1 helper epitope covalently linked to truncated P18 CTL epitope.
  - A substitution in the T1 peptide stimulated an enhanced Th response and class II binding specificity, which in turn enhanced CTL induction by vaccine.
  - Construct PCLUS 3-18MN is currently in a phase I vaccine clinical trial.
- HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (313–327 MN)  
**Epitope** RIHIGPGRAFYTTKN  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB, B clade MN *HIV component:* gp160
- Species (MHC)** mouse (D<sup>d</sup>)  
**References** Takahashi *et al.* 1989b
- Y(11 MN) exchange with V(11 IIIB) interchanges specificities.
- HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (313–327 IIIB, MN, RF)  
**Epitope** SITKGPGRVIYATGQ  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade RF  
*HIV component:* gp160
- Species (MHC)** mouse (D<sup>d</sup>)  
**References** Takahashi *et al.* 1992
- Comparison of MN, IIIB, and RF specificities, position 11 is critical.
- HXB2 Location** gp160 (308–322)  
**Author Location** gp160 (315–329 IIIB)  
**Epitope** RIQRGPGRAFVTIGK

**Epitope name** P18**Immunogen** in vitro stimulation or selection**Species (MHC)** mouse (Dd)**Donor MHC** H-2d**Keywords** TCR usage**References** Yokosuka *et al.* 2002

- The TCR repertoire and its specificity was studied through analyzing the spectrum of TCR-alpha and beta chains able to reconstitute a reaction to the H-2 Dd-restricted P18 peptide. The RT-1 TCR alpha chain was able to react with 1/3 of the tested TCR beta chains to create a specific response. Experiments in transgenic mice also supported the observation that a single TCR alpha chain would confer the specificity of the response and could interact with a large variety of TCR beta chains.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (HXB2)**Epitope** RIQRGPGRAFVTIGK**Subtype** B**Immunogen** vaccine*Vector/Type:* protein *HIV component:* Gag, V3**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Griffiths *et al.* 1993

- Gag-V3 fusion protein immunization elicited V3 CTL response in mice.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (HXB2)**Epitope** RIQRGPGRAFVTIGK**Subtype** B**Immunogen** vaccine*Vector/Type:* virus-like particle (VLP) *HIV component:* Env, Gag**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Deml *et al.* 1997

- Env bound to virus-like particles (VLPs) can elicit a CTL response that is dependent on the amount of Env presented on the VLP.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (313–327 MN)**Epitope** RIHIGPGRAFYTTKN**Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade MN *HIV component:* gp160, V3**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Fomsgaard *et al.* 1998a

- Enhanced B and CTL responses to the V3 region occur following epidermal immunization by gene gun with a chimeric DNA vaccine of V3-hepatitis B surface antigen relative to a gp160 plasmid vaccine.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (313–327 MN)**Epitope** RIHIGPGRAFYTTKN**Immunogen** vaccine*Vector/Type:* peptide *Strain:* B clade MN*HIV component:* V3 *Adjuvant:* GM-CSF, IL-12**Species (MHC)** mouse (H-2<sup>d</sup>)**Keywords** Th1**References** Ahlers *et al.* 1996; Ahlers *et al.* 1997a

- Vaccine constructs containing helper, antibody and CTL peptide epitopes induce strong Th1, CTL and NAb responses against the autologous HIV-1 virus.
- The peptide CTL response was as cross-reactive as one elicited by a vaccinia construct expressing rgp160 MN.
- GM-CSF and IL-12 were the two cytokines most effective for inducing and boosting CTLs.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Immunogen** vaccine*Vector/Type:* virus-like particle (VLP)*Strain:* B clade IIIB *HIV component:* Gag, V3**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Layton *et al.* 1993

- V3-Ty-Virus-like particles can induce type-specific CTL in mice in the absence of adjuvant.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (IIIB)**Epitope** RIQRGPGRAFVTIGK**Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade IIIB*HIV component:* gp120 *Adjuvant:* IL-2, IL-2/Ig**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Barouch *et al.* 1998

- A discistronic IL-2 gp120 expression vector gave a weaker CTL response than gp120 alone in the expression vector, however co-administration of an IL-2/IgG fusion protein enhanced the immune response and administration of a IL-2/IgG plasmid had a response that depended on the timing of administration.
- This study showed that a response to an HIV-1 DNA vaccine could be either augmented or suppressed by plasmid Cytokine/Ig administration.

**HXB2 Location** gp160 (308–322)**Author Location** Env (308–322 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen** vaccine*Vector/Type:* peptide *Strain:* B clade IIIB*HIV component:* V3 *Adjuvant:* B7, CpG immunostimulatory sequence (ISS), in vivo electroporation**Species (MHC)** mouse (H-2<sup>d</sup>)**Keywords** Th1**References** Uno-Furuta *et al.* 2001



- Peptide immunization usually doesn't elicit a good CTL response because epitopes are not internalized and processed and presented, so vaccination with electric pulsing was tried (i.m. injection followed by 8 electric pulses), to enhance peptide uptake through electroporation.
- BALB/c immunized with HIV P18 or hepatitis C P17 peptides with an electric pulse elicited a CTL response, those that did not receive the pulse did not.
- The CTL response was enhanced by addition of immunostimulatory sequences ISS in the plasmid pCMV-LacZ, that contains hexamers GACGTC, AGCGCT, AACGCT, sequences common in prokaryotic genomes but rare in eukaryotic genomes that elicit Th1 cytokines and result in B cell and T-cell proliferation.
- The CTL response was also enhanced by addition of B7-1 cDNA – the B7 family of proteins transduce co-stimulatory signals through interaction with CD28.

**HXB2 Location** gp160 (308–322)

**Author Location** gp160 (MN)

**Epitope** RIHIGPGRAFYTTKN

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade MN

*HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)

**References** Fomsgaard *et al.* 1998b

- CTL responses to a primary gene gun vaccination were rapid and strong for several methods of vaccinations: i.m., bupivacaine pretreatment, cardiotoxin pretreatment or gene gun – the CTL response was more rapid and consistent than the antibody response.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (315–329 IIIB)

**Epitope** RIQRGPGRAFVTIGK

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>p</sup>, H-2<sup>q</sup>, H-2<sup>u</sup>)

**References** Shirai *et al.* 1992; Shirai *et al.* 1993

- In a murine system multiple class I molecules can present this peptide, called P18, to CTL, including H-2D<sup>d</sup>, H-2D<sup>p</sup>, H-2D<sup>q</sup>, H-2L<sup>q</sup>
- The MHC class I molecule D<sup>d</sup> as well as H-2<sup>u,p,q</sup>, were found to present peptides P18 and HP53.
- The V-β usage in T cells showing cross-reaction between these two peptides was conserved for H-2<sup>d,u,p</sup>, but not in H-2<sup>q</sup>

**HXB2 Location** gp160 (308–322)

**Author Location** gp160 (IIIB)

**Epitope** GIHIGPGRFYAARK

**Immunogen** vaccine

*Vector/Type:* peptide, protein *Strain:* B

clade IIIB *HIV component:* gp160 *Adjuvant:* E. coli mutant heat labile enterotoxin

(LT-R72)

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Keywords** Th1, Th2

**References** Morris *et al.* 2000

- LT(R192G) induces gp160-specific serum and mucosal IgG1 and IgG2a, systemic CTL activity and Th1 and Th2 cytokine responses upon intranasal immunization.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (315–329 IIIB)

**Epitope** RIQRGPGRAFVTIGK

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

*HIV component:* V3 *Adjuvant:* Cholera toxin (CT)

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Porgador *et al.* 1997

- A intranasal peptide vaccine with cholera toxin as a mucosal adjuvant was given.
- IIIB peptide referred to as R15K.
- Peptide-specific CTLs were induced after *in vitro* restimulation with peptide-pulsed targets.
- R15K was superior at inducing CTL compared to the RGP- GRAFVTI, in contrast to the findings of Nehete *et al.*
- Memory CTL responses were induced.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (315–329 IIIB)

**Epitope** RIQRGPGRAFVTIGK

**Immunogen** vaccine

*Vector/Type:* vaccinia with H1 influenza HA

gene cassette *Strain:* B clade IIIB *HIV*

*component:* p18 Gag

**Species (MHC)** (H-2D<sup>d</sup>)

**References** Chiba *et al.* 1999

- Vaccine was capable of priming P18IIIB specific CTL in BALB/c mice, but could not induce a P18IIIB-specific antibody response.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (multiple)

**Epitope** RIHIGPGRAFYTTKN

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade MN,

B clade SC *HIV component:* V3

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Casement *et al.* 1995

- V3 peptides from MN and SC induce murine CTL that are cross-reactive with diverse strains.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (313–327 MN)

**Epitope** RIHIGPGRAFYTTKN

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade MN

*HIV component:* gp120 *Adjuvant:* QS21

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Newman *et al.* 1997

- MN vaccine induced CTL reactive with MN, IIIB and RF vaccinia-expressed Env, but not this peptide.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (315–329 IIIB)

**Epitope** RIQRGPGRAFVTIGK

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120 *Adjuvant:* QS21

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Newman *et al.* 1997

- IIIB vaccine induced IIIB type-specific CTL to this peptide (P18), and an additional Env CTL response that was cross-reactive.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (315–329)

**Epitope** RIQRGPGRAVFTIGK

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* gp160

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Takahashi *et al.* 1988

- V3 loop CTL response in mice vaccinated with gp160.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (315–329)

**Epitope** RIQRGPGRAVFTIGK

**Immunogen** vaccine

*Vector/Type:* liposome *Strain:* B clade IIIB  
*HIV component:* V3 *Adjuvant:* oligomannose

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Fukasawa *et al.* 1998

- The peptide RIQRGPGRAVFTIGK was incorporated into liposomes and given as a subcutaneous injection, which induces a MHC class I restricted CTL response in mice.
- Liposomes coated with oligomannose show no toxicity and can elicit a potent CTL response upon a single subcutaneous infection, while non-coated liposomes do not, suggesting that oligomannose may be a good adjuvant for CTL responses.

**HXB2 Location** gp160 (308–322)

**Author Location**

**Epitope** RIQRGPGRAVFTIGK

**Epitope name** P18

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* fusion protein with anthrax delivery domain *HIV component:* V3 *Adjuvant:* B. anthracis lethal toxin LF component

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Keywords** epitope processing, vaccine-specific epitope characteristics

**References** Lu *et al.* 2000a

- Bacillus anthrax lethal toxin (LFn)-HIV fusion proteins are candidate HIV vaccines that are safe in mice, and LFn-V3 region fusion proteins induce CD8 T cells in BALBc mice. LFn causes exogenous protein to be taken up and processed in a class I pathway. Expressed proteins from Gag p24 and nef fragments cloned into the LFn expression plasmid stimulate gag-specific CD4 proliferation and CTL responses in HIV-infected donor PBMCs *in vitro*.

**HXB2 Location** gp160 (308–322)

**Author Location** gp120 (V3) (MN)

**Epitope** RIHIGPGRAFYTTKN**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB  
*HIV component:* V3 *Adjuvant:* Cholera toxin (CT), GM-CSF, IL-12, IL-18, IL-1 $\alpha$

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Staats *et al.* 2001

- Cholera toxin (CT) is a potent adjuvant used in animal studies that is not safe in humans, so combinations of cytokines were used in nasal immunization of BALB/c mice V3 peptides to attempt to replace CT as a potent adjuvant.
- Peptide vaccine induced CTL activity was significantly increased by IL-1 $\alpha$ , IL-18, and GM-CSF given alone as adjuvant, but CT gave more potent CTL activity than any single cytokine.
- Combinations of cytokines could be more potent than CT as an adjuvant. The highest tetramer binding of H-2D<sup>d</sup> peptide-specific PBMC after nasal immunization was observed with IL-1 $\alpha$  plus IL-18 as adjuvant.
- Nasal immunization with HIV peptide in the presence of IL-1 $\alpha$ , IL-12 and GM-CSF induced IFN- $\gamma$ -secreting cells in the cervical lymph node, the lung and the spleen, and was associated with upregulation of MHC class II and B7.1 on nonlymphocytes in NALT/nasal mucosal cells.
- Consistent results were obtained for the IIIB and the MN peptides.

**HXB2 Location** gp160 (308–322)

**Author Location** gp160 (315–329 MN)

**Epitope** RIHIGPGRAFYTTKN

**Epitope name** P18

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Donor MHC** H-2d

**Keywords** TCR usage

**References** Yokosuka *et al.* 2002

- The TCR repertoire and its specificity was studied through analyzing the spectrum of TCR- $\alpha$  and  $\beta$  chains able to reconstitute a reaction to the H-2 D<sup>d</sup>-restricted P18 peptide. The RT-1 TCR  $\alpha$  chain was able to react with 1/3 of the tested TCR  $\beta$  chains to create a specific response. Experiments in transgenic mice also supported the observation that a single TCR  $\alpha$  chain would confer the specificity of the response and could interact with a large variety of TCR  $\beta$  chains.

**HXB2 Location** gp160 (308–322)

**Author Location** Env (IIIB)

**Epitope** RIQRGPGRAVFTIGK

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* poly(I:C), lipopolysaccharide (LPS)

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Assay type** Chromium-release assay

**Keywords** epitope processing, vaccine-induced epitopes, Th1, Th2, immunotherapy, adjuvant comparison

**References** Fujimoto *et al.* 2004

- When BALB/c mice were immunized with recombinant HIV-1 Env gp120 or Influenza HA protein together with polyriboinosinic polyribocytidylic acid (poly (I:C)), an epitope-specific CD8+ class I MHC-restricted CTL response was observed. This response was not observed when LPS was used as adjuvant instead of poly (I:C) indicating activation of cellular immunity by poly (I:C). In the presence of poly (I:C), immature DC presented processed external antigen in association with class I MHC.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (315–329 IIIB)  
**Epitope** RIQRGPGRAFVTIGK

**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160

- Species (MHC)** mouse (H-2<sup>u</sup>, H-2D<sup>d</sup>, H-2D<sup>p</sup>, H-2D<sup>q</sup>)  
**References** Shirai *et al.* 1996b
- Multiple murine MHC can cross-present this epitope (P18) and HP53, DRVIEVVQGAYRAIR, to specific CTL.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp160 (MN)  
**Epitope** RIHIGPGRAFYTTKN

**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade MN  
*HIV component:* V3 *Adjuvant:* Montanide (ISA 51)

- Species (MHC)** human  
**References** Pinto *et al.* 1999
- Peptide P18: Eight HIV+ individuals were vaccinated with peptides containing specific T helper, CTL and Ab epitopes in Montanide ISA 51 in a Phase I trial.
  - Four displayed a 4-fold increase in PCLUS 3-18 MN-specific T helper responses.
  - One patient developed a new, sustained P18MN-peptide-specific CTL response – the patient's HLA haplotype was A2,30; B53,7; Cw2,4, and anti-HLA A2 antibody did not inhibit the response, suggesting it was not A2.
  - Patients with low baseline Ab levels developed an increase of neutralizing Ab titers.
  - No significant change was observed in plasma HIV viral loads and CD4 cell counts.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (MN)  
**Epitope** RIHIGPGRAFYTTKN

- Immunogen** HIV-1 infection  
**Species (MHC)** chimpanzee  
**References** Lubeck *et al.* 1997
- Epitope-specific CTL detected in chimpanzees immunized with adenovirus-HIV-1 MN gp160 recombinant.
  - CTL response may account for protection against subsequent HIV-1 SF2 challenge in a chimpanzee lacking neutralizing antibodies.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (315–329 IIIB)  
**Epitope** RIQRGPGRAFVTIGK  
**Immunogen** HIV-1 exposed seronegative

- Species (MHC)** human  
**References** Pinto *et al.* 1995
- CTL and T helper cell reactivity in healthcare workers exposed to HIV.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (313–327 MN)  
**Epitope** RIHIGPGRAFYTTKN

- Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human  
**References** Pinto *et al.* 1995
- CTL and T helper cell reactivity in healthcare workers exposed to HIV.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (110–122)  
**Epitope** RIQRGPGRAFVTIGK

- Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade IIIB  
*Adjuvant:* FLt3 ligand (FL), GM-CSF, IL-12, IL-15, IL-2

**Species (MHC)** mouse  
**Keywords** vaccine-specific epitope characteristics  
**References** Moore *et al.* 2002a

- Intramuscular immunization of BALB/c mice with DNA vaccines carrying either gp160 or Nef in the expression vector plasmid pNGVL gave different responses – gp160 induced strong gp160-specific CTL and IFN-responses and low-titer humoral responses, and Nef generated humoral (IgG1, IgG2a) responses and IFN-responses but little CTL activity.
- Co-injection of DNA plasmids encoding cytokines and/or hematopoietic growth factors, IL2, IL-12, IL-15, Flt3 ligand (FL), and GMCSF tended to give responses that were enhanced quantitatively, but not altered qualitatively.
- Co-administration of GMCSF most strongly enhanced CTL and IFN-responses against pNGVL-gp160.
- Repeated immunization with pNGVL-Nef failed to induce CTL responses. Co-administration of IL-12 most strongly enhanced humoral and IFN $\gamma$  responses.
- FL, which enhances innate immune responses, in combination with IL-2, IL-12 or IL-15 generated with most potent Nef responses.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp140 (iiib)  
**Epitope** RIQRGPGRAFTIGK

- Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* liposome, protein *Strain:* B clade IIIB *HIV component:* oligomeric gp140 *Adjuvant:* liposome

**Species (MHC)** mouse  
**Donor MHC** H-2d  
**Assay type** proliferation, Chromium-release assay  
**Keywords** adjuvant comparison  
**References** Richards *et al.* 2004

- Mice were immunized with gp140 and an adjuvant that was an oil-in-water emulsion containing liposomes with lipid A with encapsulated antigen. Stable and unstable emulsions were found to have similar potencies of inducing antigen-specific T-cell proliferation and IgG antibodies, but stable emulsions also induced antigen-specific CTL responses. Stable emulsions had lowered IgG2a/IgG1 ratios than unstable.

**HXB2 Location** gp160 (309–317)  
**Author Location** gp120 (310–318 SF2)  
**Epitope** IYIGPGRAF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2402)

- References** Ikeda-Moore *et al.* 1997
- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
  - This peptide induced CTL in 1/4 HIV-1 + people tested.
  - IYIGPGRAF bound to A\*2402 strongly, the epitope can be processed in a vaccinia construct and presented – no specific CTL clones were obtained.

**HXB2 Location** gp160 (309–318)  
**Author Location** gp120 (314–323 CM243 subtype CRF01)  
**Epitope** ITVGPQVVFY  
**Epitope name** E309-318  
**Subtype** CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was strongly reactive in HIV+ control study subject 184 who carried HLA-A11.

**HXB2 Location** gp160 (309–318)  
**Author Location** gp120 (314–323 CM243 subtype CRF01)  
**Epitope** ITVGPQVVFY  
**Subtype** CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Keywords** subtype comparisons  
**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.

- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it.
- This epitope was not conserved in other subtypes, and exact matches were rare.

**HXB2 Location** gp160 (310–318)  
**Author Location**  
**Epitope** HIGPGRAFY  
**Epitope name** Env-HY9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3002)  
**Donor MHC** A\*3002, A\*3201, B\*4501, B\*5301, Cw\*0401, Cw\*1202  
**Keywords** HAART, ART  
**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Subject 00RCH33 was on HAART had a viral load of 2900 and CD4 count of 727 and also recognized the epitopes YPLTFGWYCY, Nef(135-143), HLA B\*5301; AETFYVDGA, RT(437-445), HLA B\*4501; and RSLYNTVATLY, p17(76-86), HLA A\*3002.
- Among HIV+ individuals who carried HLA A30, 3/16 (19%) recognized this epitope.

**HXB2 Location** gp160 (310–318)  
**Author Location** gp120 (310–318)  
**Epitope** HIGPGRAFY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3002)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** gp160 (310–318)  
**Author Location**  
**Epitope** HIGPGRAFY  
**Epitope name** Env-HY9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 6/29 (21%) recognized this epitope.

**HXB2 Location** gp160 (310–318)  
**Author Location** gp160 (313–321 WEAU)  
**Epitope** TLGPGRVLY  
**Epitope name** gp160 TY9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human

- Donor MHC** A\*2902, B\*0801, B\*4403  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** dynamics, immunodominance, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion  
**References** Jones *et al.* 2004
- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
  - The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
  - This was one of five reasonably strong responses in early infection in the patient WEAU, and the epitope sequence did not vary during the first year of the infection.
- HXB2 Location** gp160 (310–323)  
**Author Location** gp120 (315–328 MN)  
**Epitope** HIGPGRAFYTTKNI  
**Epitope name** p97  
**Immunogen** vaccine  
*Vector/Type:* canarypox prime with pseudovirion boost *Strain:* B clade IIIB, B clade MN *HIV component:* Gag, gp120, Protease
- Species (MHC)** mouse (H-2D<sup>d</sup>)  
**References** Arp *et al.* 1999
- The vaccine vCP205, canarypox vector, MN gp120 + Gag/Pro IIIB, with a HIV-1 pseudovirion boost was given to mice;
  - HIV-1 pseudovirion boost enhanced the CTL to this epitope in immunized BALB/c mice as measured by CTL lysis and IFN gamma production.
- HXB2 Location** gp160 (311–318)  
**Author Location** (MN)  
**Epitope** IGPGRIFY  
**Immunogen** vaccine  
*Vector/Type:* B. abortus complex *Strain:* B clade MN *HIV component:* V3
- Species (MHC)** mouse (H-2D<sup>d</sup>)  
**References** Golding *et al.* 2002a
- Intranasal immunization of B. abortus conjugated to V3 peptides induces mucosal IFN-gamma producing T-cell responses in BALB/c mice.
- HXB2 Location** gp160 (311–319)  
**Author Location** gp120 (311–320 IIIB)  
**Epitope** RGPGRFVT
- Subtype B**  
**Immunogen** vaccine  
*Vector/Type:* DNA, DNA with protein boost  
*Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* IL-12
- Species (MHC)** mouse (A2)  
**Keywords** vaccine-specific epitope characteristics  
**References** Kiszka *et al.* 2002
- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with a full length gp160 or with gp160deltaV3, with the V3 loop deleted. Mice given gp160deltaV3 had a broader immune response than those given gp160, with increased responses to conserved HLA-A2 epitopes in the C1 region of gp120, KLTPLCVTL, and the C-term region of gp41, SLLNATAIAV.
  - Greater resistance was conferred by the gp160deltaV3 than the gp160 vaccine to a challenge of vaccinia expressing heterologous gp160 from primary isolates (VI-06 and 89.6), and the resistance was conferred by CD8+ T-cells.
  - The most intense CTL responses to the intact gp160 vaccine were directed at three V3 peptides.
- HXB2 Location** gp160 (311–319)  
**Author Location** gp120 (312–320 SF2)  
**Epitope** IGPGRFHT  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade SF2 *HIV component:* gp120
- Species (MHC)** mouse (D<sup>d</sup>)  
**References** Selby *et al.* 1997
- Murine CTL response to peptide observed after immunization with DNA plasmid containing HIV-1 (SF2) gp120 gene regulated by bacteriophage T7 promoter.
  - CTL response required coadministration of rec vaccinia virus expressing T7 RNA polymerase or T7 RNA polymerase soluble protein.
- HXB2 Location** gp160 (311–319)  
**Author Location** gp120 (SF2)  
**Epitope** IGPGRFHT  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with gp120 boost  
*Strain:* B clade SF2 *HIV component:* gp120
- Species (MHC)** mouse (H-2D<sup>d</sup>)  
**References** Barnett *et al.* 1997
- CTL were induced by vaccine, and restimulated *in vitro* with V3 peptide.
  - DNA vaccine with protein boost stimulated both CTL and antibodies.
  - Strains SF2 (IGPGRFHT), US4 (IGPGRIFYA), and CM235 (IGPGQVFYR) were tested.
- HXB2 Location** gp160 (311–319)  
**Author Location** gp120 (312–320 SF2)  
**Epitope** IGPGRFHT  
**Subtype B**  
**Immunogen** vaccine  
*Vector/Type:* DNA, vaccinia *Strain:* B clade SF2 *HIV component:* Gag, gp120

**Species (MHC)** mouse (H-2D<sup>d</sup>)  
**Assay type** Chromium-release assay  
**Keywords** epitope processing, vaccine-induced epitopes  
**References** Doe *et al.* 1996

- Spleen cells from mice with distinct MHC types were infused into HIV vaccinated scid mice, to study the antigen presenting cells used by CTL induced in intramuscular injections. Bone marrow derived cells are used for presentation, but DNA infection is not required for priming, rather APCs can present proteins synthesized in other host cells.

**HXB2 Location** gp160 (311–320)

**Author Location** Env (311–320)

**Epitope** RGPGRGFYTT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naïve subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIB)

**Epitope** RGPGRGFVTI

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A\*0201)

**References** Alexander-Miller *et al.* 1996

- This epitope stimulates a CTL line derived from an HIV negative donor.
- This immunogenic peptide does not have the known binding motif for A2.1.
- The same optimal peptide for this human HLA-A2.1 epitope was observed for a murine H-2 D<sup>d</sup> epitope.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (311–320 IIIB)

**Epitope** RGPGRGFVTI

**Immunogen**

**Species (MHC)** human (A\*0201)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0201 epitope.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIB)

**Epitope** RGPGRGFVTI

**Epitope name** LR25

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade LAI

*Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG

**Species (MHC)** mouse (A\*0201)

**Keywords** binding affinity, vaccine-specific epitope characteristics, immunodominance

**References** Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRGFVTI and VIYQMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQMDDL induced a strong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIB)

**Epitope** RGPGRGFVTI

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* gp160

**Species (MHC)** human (A2)

**References** Achour *et al.* 1996

- Individual was immunized with rec vaccinia gp160 IIIB and boosted with purified gp160.
- Lysis only occurs with IIIB P18 peptide pulsed onto autologous targets; MN, RF, SIMI P18 peptides fail to stimulate CTL.
- Restimulating immune cells from gp160 IIIB vaccinees with MN, RF, or SIMI P18 did not enhance the MN, RF, or SIMI specific CTL response.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 SIMI)

**Epitope** MGPKRAFAT

**Immunogen** vaccine

*Vector/Type:* vaccinia prime with gp160

*boost Strain:* B clade SIMI *HIV component:* gp160

**Species (MHC)** human (A2)

**References** Achour *et al.* 1996

- Individual was immunized with rec vaccinia gp160 SIMI and boosted with purified recombinant gp160 SIMI.

- P18 MN and RF peptides were able to stimulate the HIV-specific CTL that arose in response to the SIMI vaccination, thus the P18 MN peptide (IGPGRAFYT) and the P18 RF peptide (KGPGRVIYAT) could cross-react.
- The P18 IIIB peptide does not cross-react (RGPGRAFVTI in the epitope region)
- gp160 SIMI primed immune cells could generate a significantly broader specificity when stimulated with P18 MN or P18RF peptides, but not P18 IIIB.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (311–320)

**Epitope** RGPGRAFVTI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (311–320)

**Epitope** RGPGRAFVTI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding

**Keywords** acute/early infection, optimal epitope

**References** Altfield *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was recognized both in acute and chronic infection, but slightly more frequently in chronic infection.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120

**Epitope** RGPGRAFVTI

**Epitope name** A2-RII0(gp120)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIB)

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

*HIV component:* V3

**Species (MHC)** mouse (D)

**References** Nehete *et al.* 1995

- RGPGRAFVTI was defined as the optimal peptide for vaccination, out of RIQRGPGRAFVTIGK.
- This peptide, in a carrier-free form in Freund's adjuvant, could stimulate Env specific CTL in BALB/c mice.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIB)

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

*HIV component:* V3

**Species (MHC)** mouse (D<sup>d</sup>)

**Keywords** dendritic cells

**References** Takahashi *et al.* 1993

- Successful priming with vaccination of peptide pulsed splenic dendritic cells.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIB)

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

*HIV component:* V3

**Species (MHC)** mouse (D<sup>d</sup>)

**References** Takahashi *et al.* 1996

- Exposure of CD8+ CTL to free peptide corresponding to the epitope results in strong inhibition of the CTL response to targets presensitized with the same peptide.
- The authors propose this is due to a "self-veto", where the CTL is inactivated by a CD8+ cell carrying the appropriate peptide-MHC complex.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* vaccinia

**Species (MHC)** mouse (H-2<sup>d17</sup>)

**References** Hanke *et al.* 1998a

- MVA is an attenuated vaccinia that can not replicate in mammalian cells – strings of CTL epitopes were delivered and expressed in a MVA DNA vector.

- INF $\gamma$  and CTL activity were induced after a single vaccination.
- An MVA boost enhanced the response.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* DNA, vaccinia *HIV component:* Env *Adjuvant:* IL-12

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Gherardi *et al.* 2000

- Induction of HIV-1 specific CD8 gamma IFN secreting cells was enhanced when IL-12 and Env were given together in a prime, followed by a VV expressing Env boost.
- If IL-12 was also delivered as a boost from the viral vector, impairment of the IL-12 effects was noted, indicating that the vaccination schedule can be a critical parameter for success with DNA and vaccinia vectors used in combination with immunomodulators.
- The negative effect observed when IL-12 was delivered with the boost involved nitric oxide.

**HXB2 Location** gp160 (311–320)

**Author Location** Env

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* IL-12, IL-15, IL-2

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** Th1

**References** Xin *et al.* 1999

- A study of the DNA vaccine pCMV160IIIB/REV with IL-15 and IL-2 or IL-12 expression plasmids.
- Intranasal immunization of BALB/c mice with HIV DNA and IL-15 plasmid induced increased Th1 and CTL responses.
- Co-administration of IL-15 with IL-12 or IL-2 plasmids did not alter the effect of IL-15.
- Both the CTL (peptide pulsed targets) and DTH response (injection of peptide into footpad) to this peptide was monitored.
- The Ab response to NNTRKSIRIQRGPGRAFVTIGKIGN was monitored, and IL-15 co-administration resulted in a decrease in the IgG1/IgG2a ratio.

**HXB2 Location** gp160 (311–320)

**Author Location** Env

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* vaccinia, Sindbis *HIV component:* V3

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Villacres & Bergmann 1999

- HIV-1 epitope p18 was expressed in two different vaccine vectors and the CTL response was compared in BALB/c mice.
- Class I tetramer staining showed that up to 13% of the CD8+ splenocytes were p18 specific in the acute response using vaccinia, only 4% using Sindbis.
- vp18 had more gamma IFN secreting splenocytes and activated CD4+ and CD8+ T cells.

- The overall decline in CD8+ T cells in the transition into memory was 2–3 fold for both vectors.
- Sindbis virus recombinants induced protective memory cytotoxic T cells, although reduced quantitatively, without vaccinia associated inflammation and replication.

**HXB2 Location** gp160 (311–320)

**Author Location** Env (318–327)

**Epitope** RGPGRAFVTI

**Immunogen**

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** epitope processing, immunodominance

**References** Lopez *et al.* 2000

- A series of protease and proteasome inhibitors was used to identify elements of the processing pathway of this epitope, called p18, both from within Env and from within a chimeric hepatitis B protein which allows proper processing.
- Lactacystin, a proteasome inhibitor, partially inhibits endogenous processing of p18 epitope suggesting both a proteasome pathway and an additional pathway can be used.
- Both TAP dependent and TAP-independent pathways can be used.
- 1,10-phenanthroline (metallopeptidases inhibitor) blocks epitope presentation demonstrating metalloproteinase processing in the Tap-dependent pathway.
- The Tap-independent pathway does not involve processing by metalloproteinases.
- This epitope is immunodominant in mice, and is presented by multiple human HLA alleles – it has been suggested that the high processing efficiency of this epitope might result in poor presentation of co-expressed epitopes.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* vaccinia

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hanke *et al.* 1998a; Hanke *et al.* 1998b

- This murine epitope was incorporated into a vaccine of CTL epitopes expressed together including 20 HIV epitopes recognized by humans from 12 HLA types, one murine HIV epitope and three macaque HIV epitopes, delivered in a vaccinia virus Ankara (VVA) construct.
- The murine vaccination was more effective at generating CTL when given i.v. rather than i.m.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIB)

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* CD4BS, HPG30, V3 *Adjuvant:* IL-12

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hamajima *et al.* 1997

- B cell epitope HGP-30 also serves as a CTL epitope.
- Vaccine combined HGP-30, V3 loop peptide variants, and CD4 binding site peptide.
- IL-12 expression plasmid included with the vaccination enhanced the CTL response.



**HXB2 Location** gp160 (311–320)  
**Author Location** gp160 (318–327 IIIB)  
**Epitope** RGPGRAFVTI  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade IIIB  
*HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Keywords** Th1, Th2  
**References** Arai *et al.* 2000

- Low-dosage 8 Br-cAMP given in combination with a DNA vaccine to BALB/c mice increased IgG and sIgA levels, and enhanced Th1, Th2 and CTL activity – the adjuvant activity may be mediated by activation of the CMV promoter in the DNA vaccine.

**HXB2 Location** gp160 (311–320)  
**Author Location** gp120 (318–327 IIIB)  
**Epitope** RGPGRAFVTI  
**Immunogen** vaccine  
*Vector/Type:* fusion protein with anthrax delivery domain *HIV component:* gp120  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**References** Goletz *et al.* 1997

- Anthrax lethal toxin can deliver proteins to the cytosol of eukaryotic cells.
- A fusion protein linking the delivery domain of the anthrax protein to gp120 achieved cellular uptake, and gp120 was processed allowing presentation of this V3 epitope to CTL *in vitro*.

**HXB2 Location** gp160 (311–320)  
**Author Location** gp160 (318–327 IIIB)  
**Epitope** RGPGRAFVTI  
**Epitope name** I-10  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**References** Takahashi *et al.* 2001

- Pre-incubation of HIV-1 (IIIB) gp160 specific CTL with peptide without APCs reduced cytolytic activity 3.5 fold and induced peptide concentration dependent IL-2 unresponsiveness that might be due to IL-2Rbeta down regulation.
- An enhanced cytolytic activity was observed by addition of anti-IFN-gamma, TNF-alpha or MIP-1beta to I-10 suppressed CTLs.

**HXB2 Location** gp160 (311–320)  
**Author Location** gp160 (IIIB)  
**Epitope** RGPGRAFVTI  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Keywords** Th1, Th2  
**References** Shirai *et al.* 2001

- Helicobacter pylori induces Th1 responses early, but predominantly Th2 responses later in infection (at 6 weeks) – differentiation of HIV-1 gp160 CD4+ help and CD8+ CTL effector cells in response to HIV gp160-vaccinia vaccination is impaired in BALB/c mice infected with H. pylori.

**HXB2 Location** gp160 (311–320)  
**Author Location** gp120 (V3) (IIIB)  
**Epitope** RGPGRAFVTI  
**Immunogen** vaccine  
*Vector/Type:* influenza *Strain:* B clade IIIB  
*HIV component:* V3  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Assay type** Intracellular cytokine staining, Chromium-release assay  
**Keywords** genital and mucosal immunity, memory cells, vaccine antigen design  
**References** Garulli *et al.* 2004

- BALB/c mice were transiently infected vaginally with a recombinant influenza virus expressing an HIV CTL V3 epitope. Infection was promoted by prior progesterone treatment. This vaccination induced long-term cellular T-cell responses in mice. Responses were induced at both local mucosal and systemic sites against both influenza and V3 epitopes. Intranasal vaccination also resulted in T-cell responses in distant mucosal tissues.

**HXB2 Location** gp160 (311–320)  
**Author Location** gp120 (318–327 IIIB)  
**Epitope** RGPGRAFVTI  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>p</sup>, H-2<sup>u</sup>)  
**References** Shirai *et al.* 1997

- Three class I MHC, H-2<sup>d,p,u</sup>, that differ in sequence and serology, cross-present this peptide to T cells of each of the other haplotypes.
- The amino acids R, F, and I are each critical for strong CTL activity with all three MHC molecules.

**HXB2 Location** gp160 (311–320)  
**Author Location** Env (89.6)  
**Epitope** IGPGRARYAR  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade 89.6  
*HIV component:* gp160  
**Species (MHC)** mouse (H-2D)  
**References** Belyakov *et al.* 1998b

- Recombinant modified vaccinia virus Ankara (MVA), an attenuated vaccinia which has lost the ability to replicate in mammalian cells, was used as the live vector for this vaccine study.
- A single intrarectal mucosal immunization resulted in long lasting mucosal CTL responses and production of proinflammatory cytokines in mucosal sites, indicating that MVA was as effective in inducing mucosal CTL as replicating recombinant vaccinia.

**HXB2 Location** gp160 (311–320)  
**Author Location** Env (IIIB)  
**Epitope** IGPGRARYAR  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade IIIB  
*HIV component:* V3  
**Species (MHC)** mouse (H-2D)  
**References** Belyakov *et al.* 1998a

- HIV protection and mucosal CTL response was studied – an HIV peptide immunogen could protect against gp160 expressing vaccinia in a murine intrarectal challenge system in which neutralizing Abs did not play a role, demonstrating mucosal CTL at the site of exposure can be protective.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (MN)

**Epitope** IGPGRAFYTT

**Immunogen** vaccine

*Vector/Type:* B. abortus complex

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Lapham *et al.* 1996

- B. abortus-peptide conjugate induced a virus-specific CTL response in CD4+ lymphocyte depleted mice.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (IIIB)

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* non-replicating adenovirus

*Strain:* B clade IIIB *HIV component:* Env,

Rev

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Bruce *et al.* 1999

- A good HIV-1 Env immune response using non-replicating adenovirus vectors in BALB/c mice is dependent upon the presence of the stimulatory tat/rev 5' splice-donor site sequence and the presence of Rev.
- Administration of monocistronic RAd501 expressing env and RAd46 expressing rev resulted in a positive CTL response, but required two immunizations for a CTL response comparable to that induced by the bicistronic virus RAd142.
- Administration of RAd501 alone gave a low CTL response, but no humoral response, suggesting a lower level of antigen may be required to stimulate CTL.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (MN)

**Epitope** IGPGRAFYTT

**Immunogen** vaccine

*Vector/Type:* B. abortus complex

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Lapham *et al.* 1996

- B. abortus-peptide conjugate induced a virus-specific CTL response in CD4+ lymphocyte depleted mice.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIB)

**Epitope** RGPGRAFVTI

**Immunogen** peptide-HLA interaction

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Takeshita *et al.* 1995

- XGPXRXXXI are critical for binding, consistent with H-2D<sup>d</sup> motif XGPX(RKH)XXX(X)(LIF)

**HXB2 Location** gp160 (311–320)

**Author Location** Env

**Epitope** RGPGRAFTVTI

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* V3

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Hanke & McMichael 1999; Hanke *et al.* 1999

- Vaccinated mice elicited a CTL response to a gene gun-delivered multi-epitope vaccine to two epitopes studied that are known to elicit CTL in mice: SYIPSAEKI from Plasmodium berghei and RGPGRAFTVTI from HIV-1 Env.
- Different vaccination protocols were tested and it was found that a gene gun mediated delivery followed by an MVA boost was as good as i. m. immunization followed by a MVA boost – this is advantageous as gene gun delivery requires far less DNA than i.m. DNA priming.
- CTL activity was high (60% - 70% specific lysis at effector target) when vaccinated with a single gene gun immunization and an MVA boost, and improved with two gene gun vaccinations.

**HXB2 Location** gp160 (311–320)

**Author Location** Env (IIIB)

**Epitope** RGPGRAFVTI

**Epitope name** I-10

**Immunogen** in vitro stimulation or selection

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Keywords** epitope processing, immunodominance

**References** Nakagawa *et al.* 2000

- The CTL line LINE-IIIB was generated by repetitive restimulation of BALB/c spleen cells with vSC-25, IIIB gp160-expressing vaccinia.
- RGPGRAFVTI represents the active minimal epitope within the previously described immunodominant epitope P18IIIB (RIQRGPGRAFVTIGK, gp160(308-322))
- External processing of P18IIIB results in the removal of the 2 C-terminal residues (GK) of I-10 by ACE (angiotensin-1-converting-enzyme) in sera to produce I-10, and this processing is essential for target cell presentation of RIQRGPGRAFVTIGK.

**HXB2 Location** gp160 (311–320)

**Author Location** Env (IIIB)

**Epitope** RGPGRAFVTI

**Epitope name** p18-II10

**Immunogen** vaccine

*Vector/Type:* vaccinia, vesicular stomatitis

virus (VSV) *Strain:* B clade HXB2, B

clade IIIB *HIV component:* Env, Gag

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Keywords** immunodominance

**References** Haglund *et al.* 2002a

- Different HIV strains were used for different regions: Env IIIB, Gag HXB2
- BALB/c mice were vaccinated with rec vesicular stomatitis virus (rVSV) expressing either HIV-1 Gag, Env, or both, and compared to using rec Env and Gag in vaccinia virus (rVVs). The primary response was determined by cell lysis, cytokine production and tetramer staining.

- Primary CTL responses to the immunodominant Env (RGP- GRAFVTI) epitope peaked 5-7 days after intraperitoneal vaccination with Env-rVSV, 40% of the CD8+ cells were tetramer positive, and this response was 6-fold higher than the response to Env-rVV.
- Vaccinating with GagEnv-rVSV carrying both Gag and Env allowed recognition of both HIV-1 proteins, but at reduced levels compared to either Gag-rVSV or Env-rVSV alone.
- Intranasal immunization with Env-rVSV yielded CTL responses that were strong but reduced compared to an intraperitoneal route.

**HXB2 Location** gp160 (311–320)

**Author Location** Env (IIIB)

**Epitope** RGPGRAFVTI

**Epitope name** p18-I10

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vaccinia, vesicular stomatitis virus (VSV) *Strain:* B clade HXB2 *HIV component:* Env, Gag

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Keywords** immunodominance

**References** Haglund *et al.* 2002b

- Different HIV strains were used for different regions: Env IIIB, Gag HXB2
- BALB/c mice were vaccinated with rec vesicular stomatitis virus (rVSV) expressing either HIV-1 Gag or Env, or both, and retention of memory responses and recall responses were studied by tetramer staining and IFN-gamma production.
- Seven months after vaccination with Env-rVSV, 6% of the CD8+ cells were tetramer positive for the immunodominant Env epitope; these cells had a memory phenotype, CD44-Hi positive.
- Env in rec vaccinia virus (Env-rVV) elicited a strong recall response, with up to 45% to the CD8+ T-cell population tetramer positive and activated (expressing CD62L-Lo), and capable of IFN-gamma production.
- A prime with Env-rVSV and heterologous boost of Env-rVV gave remarkably high levels of memory cells, with approximately 1/3 of the CD8+ splenocytes being Env specific memory cells 150 days after the boost.
- A Gag-rVSV or EnvGag-rVSV prime and with a heterologous Gag-rVV or EnvGag-rVV boost combination gave 40% tetramer positive CD8+ cells, but the fraction of IFN-gamma producing cells was only about 25%. Still the heterologous vector prime-boost combination showed a profound benefit.
- A HIV-1 protein rVSV prime, rVV boost was a more potent combination than a vector reversal of a rVV prime and rVSV boost.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (V3) (IIIB)

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB *HIV component:* V3 *Adjuvant:* Cholera toxin (CT), GM-CSF, IL-12, IL-18, IL-1 $\alpha$

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Staats *et al.* 2001

- Cholera toxin (CT) is a potent adjuvant used in animal studies that is not safe in humans, so combinations of cytokines were used in nasal immunization of BALB/c mice V3 peptides to attempt to replace CT as a potent adjuvant.
- Peptide vaccine induced CTL activity was significantly increased by IL-1 $\alpha$ , IL-18, and GMCSF given alone as adjuvant, but CT gave more potent CTL activity than any single cytokine.
- Combinations of cytokines could be more potent than CT as an adjuvant. The highest tetramer binding of H-2Dd peptide-specific PBMC after nasal immunization was observed with IL-1 $\alpha$  plus IL-18 as adjuvant.
- Nasal immunization with HIV peptide in the presence of IL-1 $\alpha$ , IL-12 and GM-CSF induced IFN-gamma-secreting cells in the cervical lymph node, the lung and the spleen, and was associated with upregulation of MHC class II and B7.1 on nonlymphocytes in NALT/nasal mucosal cells.
- Consistent results were obtained for the IIIB and the MN peptides.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIB)

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* beta-glucan lentinan, IL-2/Ig, liposome, PLG

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Keywords** immunodominance

**References** Wierzbicki *et al.* 2002

- BALB/c mice were given an oral immunization with (PLG)-encapsulated plasmid DNA expressing gp160 and a boost of rec gp160 vaccinia vectors (rVV) with addition of murine IL-2/Ig plasmid or lentinan-associated liposomes. Lentinan increased CTL activity as measured by Cr-release assays against the immunodominant epitope RGPGRAFVTI, but didn't alter Ab responses. IL-2/Ig increased both type I and II activities, and increased Env specific CTL and Abs. Administration of liposomes and PLG microparticles with adjuvants facilitated gastrointestinal uptake.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (LAI)

**Epitope** RGPGRAFVTI

**Epitope name** P18

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI *HIV component:* Gag, gp120 *Adjuvant:* CpG immunostimulatory sequence (ISS)

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**References** Horner *et al.* 2001

- Immunostimulatory sequences (ISS), also known as CpG motifs, stimulate innate immunity and enhance vaccine-specific immune responses.
- Intranasal immunization (i.n.) of BALB/c mice was more effective than intradermal (i.d.), and immunization with a gp120-ISS conjugate was more potent than immunizing with gp120 and separate ISS molecule – increased IgG1, IgG2a,

IFN-gamma, MIP1-alpha and MIP1-beta production was observed, and only i.n. immunization gave IgA responses.

- The highest mucosal CTL activity in both the Lamina Propria and the Peyer's Patch was observed following intranasal delivery with the gp120/ISS conjugate.
- Cytokine, chemokine and CTL responses following gp120/ISS conjugate vaccination were CD4+ T-cell independent; gp120 specific antibodies were dependent on helper T cells.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (V3) (IIIB)

**Epitope** RGPGRAFVTI

**Epitope name** I10

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* gp160

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Keywords** acute/early infection

**References** Takahashi *et al.* 2002

- During acute infection, high doses of virus result in "clonal exhaustion", a depletion of antigen specific T-cells.
- Recently stimulated CTL from BALB/c mice vaccinated with gp160-vaccinia showed a dose- and time-dependent induction of apoptosis when stimulated with antigenic peptide or H-2Dd/peptide tetramers.
- Restimulated CTL showed an upregulation of CD3-chain phosphorylation in comparison to cells stimulated with target cells, indicative of TCR-mediated apoptosis. Furthermore, apoptosis was inhibited by cyclosporin A and U0126, a mitogen activated kinase inhibitor specific for the ERK1/ERK2 MAPK kinase pathway, and a caspase 3 inhibitor.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (V3) (MN)

**Epitope** IGPGRAFYAT

**Epitope name** MNT10

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* gp160

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Keywords** acute/early infection

**References** Takahashi *et al.* 2002

- During acute infection, high doses of virus result in "clonal exhaustion", a depletion of antigen specific T-cells.
- Recently stimulated CTL from BALB/c mice vaccinated with gp160-vaccinia showed a dose- and time-dependent induction of apoptosis when stimulated with antigenic peptide or H-2Dd/peptide tetramers.
- Restimulated CTL showed an upregulation of CD3-chain phosphorylation in comparison to cells stimulated with target cells, indicative of TCR-mediated apoptosis. Furthermore, apoptosis was inhibited by cyclosporin A and U0126, a mitogen activated kinase inhibitor specific for the ERK1/ERK2 MAPK kinase pathway, and a caspase 3 inhibitor.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (V3) (HIV-IIIB)

**Epitope** RGPGRAFVTI

**Epitope name** P18-I10

### Subtype B

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* gp160 *Adjuvant:* IL-15, IL-2

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Donor MHC** H-2d

**Assay type** Cytokine production, Tetramer binding, Chromium-release assay

**References** Oh *et al.* 2003a

- IL-2 and IL-15 in vaccinia constructs were given with an HIV gp160 vaccinia vaccine to BALB/c mice. Both IL-2 and IL-15 induced strong and long-lasting antibody responses. Short-term CTL responses against HIV gp120 were enhanced by IL-2, but IL-15 enhanced both immediate CD8+ T cell responses and CD8+ T memory cells.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (IIIB)

**Epitope** RGPGRAFVTI

**Epitope name** P18-I10

**Subtype B**

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* V3 *Adjuvant:* B7, ICAM, LFA-3

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Donor MHC** H-2d

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**References** Oh *et al.* 2003b

- BALB/c mice were vaccinated with T-cell depleted splenocytes pulsed with peptides given in combination with immunostimulatory molecules B7, ICAM or LFA expressed in a recombinant pox virus. Increasing antigen gave an increased frequency of CD8+ T-cells, but the co-stimulatory molecules increased the avidity of the response.

**HXB2 Location** gp160 (311–320)

**Author Location** (89.6)

**Epitope** IGPGRAFYAR

**Subtype B**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* gp120

*Adjuvant:* Flex, a dendric cell growth factor

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Donor MHC** H-2d

**Assay type** Intracellular cytokine staining

**Keywords** dendritic cells

**References** Sailaja *et al.* 2003

- BALB/c mice were given a DNA vaccine that contained gp120 DNA covalently attached to the extracellular domain of the Fms-like tyrosine kinase receptor-3 ligand (FLex), a dendritic cell growth factor.
- Mice vaccinated i.m. with the FLex:gp120 chimeric gene gave a DC expansion similar to native Flex protein.
- gp120-specific stable CD8+ T-cell responses lasted 114 days after a prime/boost, and were observed in the presence and absence of Flex-DNA-induced dendritic cell (DC) expansion; strong Ab responses required DC expansion.

**HXB2 Location** gp160 (311–320)  
**Author Location** gp120 (V3)  
**Epitope** RGPGRAFVTI  
**Immunogen** vaccine  
*Vector/Type:* herpes simplex virus type-1 (HSV-1) amplicon *HIV component:* gp120

**Species (MHC)** mouse (H-2D<sup>d</sup>)  
**Donor MHC** H-2d  
**Assay type** Tetramer binding, JAM cytotoxicity assay  
**Keywords** kinetics, memory cells  
**References** Wang 2003

- Prime-boost combinations of gp120 combined with herpes simplex virus type-1 (HSV-1) amplicon particles, or gp120 in naked amplicon plasmid DNA, were compared in BLAB/c mice. Plasmid prime with particle boosts gave the strong primary (2 weeks) and memory responses (4 months).
- CD8+ T-cells reached their peak 8-28 days after the initial amplicon delivery.

**HXB2 Location** gp160 (311–320)  
**Author Location** gp120 (V3)  
**Epitope** RGPGRAFVTI  
**Epitope name** P18-I10  
**Immunogen** vaccine  
*Vector/Type:* peptide, vaccinia *Strain:* B clade 89.6, B clade IIIB *HIV component:* gp160ΔV3 *Adjuvant:* Cholera toxin (CT), E. coli mutant heat labile enterotoxin (LT-R72), Incomplete Freund's Adjuvant (IFA), CpG immunostimulatory sequence (ISS)

**Species (MHC)** mouse (H-2D<sup>d</sup>)  
**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** dendritic cells, Th1, Th2, genital and mucosal immunity  
**References** Belyakov *et al.* 2004

- Transcutaneous immunisation (TCI) of BALB/c mice induced adjuvant-dependent HIV-1 specific CTL responses in the spleen and the gut mucosa that resulted in protection against mucosal challenge against a recombinant vaccinia virus carrying HIV-1 env. Activated DCs from skin were shown to migrate to immune-inductive sites in gut mucosa and to present antigen directly to resident lymphocytes.

**HXB2 Location** gp160 (311–320)  
**Author Location** gp120 (V3)  
**Epitope** RGPGRAFVTI  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* herpes simplex virus type-1 (HSV-1) amplicon *Strain:* B clade LAI, B clade MN *HIV component:* gp120

**Species (MHC)** mouse (H-2D<sup>d</sup>)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, JAM cytotoxicity assay  
**Keywords** vaccine antigen design  
**References** Hocknell *et al.* 2002

- BALB/c mice were immunized with HSV amplicons containing HIV-1 gp120. Helper virus free HSV-1 amplicon particles are capable of inducing potent cytotoxic CD8+ T-cell and humoral immune responses to the HIV-1 antigen in mice. Previous infection with wild-type HSV-1 reduces amplicon-induced cellular immune responses to HIV gp120 modestly (40-60%), but severally reduced B-cell responses. The route of vaccination impacted the nature and level of the responses (i.m., i.d., and i. p.).

**HXB2 Location** gp160 (311–320)  
**Author Location** gp120  
**Epitope** RGPGRAFVTI  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA, polyepitope *Strain:* B clade MN *HIV component:* gp120, Protease, RT *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** humanized mouse (H-2D<sup>d</sup>)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance, immunotherapy  
**References** Isaguliants *et al.* 2004

- Immunization of HLA-A\*0201-transgenic mice with synthetic genes encoding clusters of human A\*0201 CTL epitopes located at the sites of drug resistance mutations, induced RT-specific cellular responses indicating the immunogenicity of these constructs. This vaccine strategy may be a first step towards a therapeutic vaccine against drug-resistant strains. This epitope was included as a mouse marker for a CD8+ T-cell response.

**HXB2 Location** gp160 (311–320)  
**Author Location**  
**Epitope** RGPGRAFVTI  
**Epitope name** R10I  
**Immunogen** vaccine  
*Vector/Type:* DNA, virus-like particle (VLP), polyepitope *HIV component:* Gag, p24 Gag, V3

**Species (MHC)** mouse (H-2D<sup>d</sup>)  
**Assay type** Cytokine production, Chromium-release assay  
**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance  
**References** Wild *et al.* 2004

- A codon optimized gag DNA vaccine was compared to a myristylation defective gag and p24 alone, both of which lack signals for secretion from transfected cells. Gag-derived immunogens that were secreted as VLPs and those that remained intracellular (p24) each produced strong CTL responses, and neither the size of antigen nor cellular trafficking and localization significantly influenced the strength of humoral and cellular immune activation. The formation and release of VLPs was not essential for eliciting strong CTL. BALB/c mice were given the DNA vaccine by i.m. administration of plasmid DNA for the prime and boost.

- Linking the region encoding the V3 immunodominant epitope to the gag gene did not diminish the response to the Gag p24 epitope A9I, but did enable a response to the V3 epitope.
- Minigenes were made incorporating just 1 epitope, minitopes, carrying 1 of 3 murine class I epitopes linked to the Ad2-E3 protein-derived signal peptide to allow access of the epitope to the ER. Weak induction of cellular immune responses was observed, in contrast to the complex polyprotein.

**HXB2 Location** gp160 (311–320)

**Author Location** Env (318–327)

**Epitope** RGPGRAFVTI

**Epitope name** R10I

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* gp160

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Donor MHC** H-2D

**Assay type** Intracellular cytokine staining

**Keywords** vaccine antigen design

**References** Samino *et al.* 2004

- The endogenous processing of the HIV-1 envelope glycoprotein generates several different natural peptidic species presented by the H-2D molecule in infected cells, the 9-, 10-, and 11-mer peptides, GPGRAFVTI, RGPGRAFVTI, and QRGPGRAFVTI. CTL with the same antigenicity could recognize all three forms. The complexity of the binding peptides suggests naturally processed proteins could provide more variety as antigens, stimulating more robust and diverse CTL responses.

**HXB2 Location** gp160 (311–320)

**Author Location** p18 (IIIB)

**Epitope** RGPGRAFVTI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor

*Strain:* B clade IIIB *HIV component:*

gp120 *Adjuvant:* IL-12

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Donor MHC** H-2D

**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, memory cells, characterizing CD8+ T cells

**References** Seaman *et al.* 2004

- Delivery of plasmid IL-12 on day 10 after immunization of mice with an HIV-1 gp120 DNA vaccine resulted in expansion of gp120-specific CD8+ T-cells but had no effect on antigen-specific CD4+ T-cells and antibody responses. gp120-specific CD8+ T-cells were shown to primarily be effector memory and not central memory T-cells and did not expand following gp120 boost immunization.

**HXB2 Location** gp160 (311–320)

**Author Location** Env (gp160) (318–327 HIV-1 IIIB)

**Epitope** RGPGRAFVTI

**Epitope name** P18-I10

**Immunogen** peptide-HLA interaction

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Assay type** Chromium-release assay, Other

**Keywords** binding affinity, structure

**References** Nakagawa *et al.* 2007

- To study the critical amino acids of both TCR and MHC that interact with peptide P18-I10 of HIV-1 IIIB, the authors used a series of mutant substituted peptides. Peptides substituted with Ala at various positions showed that positions 322R, 324F and 327I were essential for binding to H2-D<sup>d</sup>. Residue 325V was critical for interacting with TCR. By employing D-amino acid derived peptides as mutants in order to avoid charge, size and molecular weight differences, they also show that 325V is necessary for CTL-induced cytotoxic activity. Using two distinct CTL clones and molecular modeling they determined that TCR sequences of CDR1 and not CDR3 critically interact with 325V.
- This 10-residue minimally active peptide lies within the immunodominant epitope, RIQRGPGRAFVTIGK, that belongs to gp160, the hypervariable region of Env. Substituted peptides used in this study were RGPGRAFiTI, RGPGRAFITi, RGPGRAFaTi, RGPGRAFyTi, RGPGRAFfTi, RGPGRAFhTi, RGPGRAFrTi, RGPGRAFsTi, RGPGRAFeTi, RGPGRAFkTi, RGPGRAFrTi and RGPGRAFpTi. In addition, D-amino acid variants of the residues in parentheses were used - (r)GPGRAFVtI, RG(p)GRAFVtI, RGPg(r)AFVtI, RGPGR(a)FVtI, RGPGRa(f)VtI, RGPGRAF(v)tI, RGPGRAFV(t)i, RGPGRAFVt(i), RGPGRAF(i)tI, RGPGRAF(I)tI, RGPGRAF(a)tI, RGPGRAF(y)tI, RGPGRAF(f)tI, RGPGRAF(h)tI and RGPGRAF(t)tI.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120

**Epitope** RGPGRAFVTI

**Epitope name** H

**Subtype** A

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost, Other *Strain:* A clade, B clade, C clade Du422, Other *HIV component:* Gag, Nef, RT

**Species (MHC)** mouse (H-2D<sup>d</sup>)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism

**References** Larke *et al.* 2007

- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.

- No cross-reactivity was seen with epitope variants (iGPGqAFyAt, fGPGqAFyTn, iPGGRAFYtT, iGPGqt-FyAt, iGIgqAlyTt, lGPGqAFyAt, iPGGRAFYAt, iGPGqvFyrt, mGPGRvFyTt) after immunization with Clade A containing index Epitope H, RGPGRAFVTI.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120

**Epitope** RGPGRAFVTI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade IIIIB, SIV *HIV component:* gp120

**Species (MHC)** macaque, mouse (H-2Dd)

**Assay type** proliferation, Tetramer binding, CD4 T-cell  
Elispot - IFN $\gamma$ , Chromium-release assay,  
Other

**Keywords** adjuvant comparison, vaccine antigen design,  
SIV

**References** Fuller *et al.* 2007

- HIV-epitope, RGPGRAFVTI, was fused to a Hepatitis B core antigen (HBcAg) gene in order to improve immunogenicity of an epitope-based vaccine in mice. A vaccine containing hybrid HBcAg-epitope linked to an HIV-specific T helper epitope induced significantly higher responses than a hybrid HBcAg-epitope vaccine which performed better than epitope alone. The authors suggest that HBcAg could be a better carrier of foreign epitopes than even Hepatitis B surface antigen (HBsAg) - (previously studied).
- This work also deals with a multi-epitope SIV-based vaccine in non-human primates.

**HXB2 Location** gp160 (311–320)

**Author Location** Env

**Epitope** RGPGRAFVTI

**Subtype** A, B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* A clade, B clade  
*HIV component:* Env, Gag

**Species (MHC)** mouse (H-2d)

**Country** Finland

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-  
release assay

**Keywords** vaccine antigen design

**References** Malm *et al.* 2007

- A novel mouse model was used to test the efficacy of 2 HIV DNA vaccines in protection against tumor challenge. Comparable immunogenicity between the single and multi-clade vaccines tested was seen in different mouse strains. CTL response to HIV-1-APCs was both in vivo and in vitro and this animal model was safe and not only evaluated vaccine immunogenicity but also confirmed the potency of GTU-multi-HIV vaccines.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIIB)

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIIB  
*HIV component:* Env, Nef

**Species (MHC)** mouse (L<sup>d</sup>)

**References** Tobery & Siliciano 1997

- An HIV-1 Env vaccine was targeted for rapid cytoplasmic degradation.
- The rapidly degraded form rapidly stimulated CTL to this peptide, faster than the normal vaccinia-env.
- The rapidly degraded form also stimulated greater specific CTL lysis and higher CTLp frequencies than normal Env.
- Similar results were obtained for a Nef protein designed for rapid degradation.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160 (318–327 IIIIB)

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* DNA prime with peptide boost  
*Strain:* B clade IIIIB *HIV component:*  
CD4BS, gp160, HPG30, V3

**Species (MHC)** macaque

**References** Okuda *et al.* 1997

- Murine BALB/c (H-2<sup>d</sup>) and macaque both showed highest level of CTL vaccine response when a DNA vaccine was boosted with a peptide including four peptide subtypes of the V3 region, HPG-30 and a fragment of the CD4 binding region.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (318–327)

**Epitope** RGPGRAFVTI

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Kmiecik *et al.* 1998b

- Increased CTL response to cells expressing a VV construct  $\Delta$ V3 mutant compared with a full-length env gene product.
- This epitope doesn't have A2 anchors, but has features that confer promiscuous A2 binding, which may relate to the inhibitory effect seen in this paper.

**HXB2 Location** gp160 (311–320)

**Author Location** Env (IIIIB)

**Epitope** RGPGRAFVTI

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade IIIIB  
*HIV component:* gp160, Rev *Adjuvant:*  
MIP-1 $\alpha$

**Species (MHC)** mouse

**References** Lu *et al.* 1999

- MIP-1 $\alpha$  co-inoculation increased IgG1/IgG2a ratio T-helper type 1 response.
- A MIP-1  $\alpha$  expression plasmid increased the CTL response to this DNA vaccine, as well as the T help response, presumably by the MIP-1  $\alpha$  interacting with T lymphocytes and macrophages.

**HXB2 Location** gp160 (311–320)

**Author Location**

**Epitope** RGPGRAFVTI

**Epitope name** P18

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade BH10  
*HIV component:* gp120 *Adjuvant:* GM-CSF

**Species (MHC)** mouse

**References** Barouch *et al.* 2002

- gp120 encoding DNA co-injected with a plasmid carrying GMCSF gave meager CD4+ T-cell responses in BALB/c mice relative to the enhanced response to bicistronic gp120 and GMCSF cloned into the same vector and expressed from the same promoter.
- Both mono and bicistronic DNA vaccines induced similar CTL responses directed against the H-2Dd restricted P18 peptide RGPGRAFTVTI in murine splenocytes despite the greatly enhanced proliferative responses.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (313–322 BRU)

**Epitope** RGPGRAFTVTI

**Epitope name** Pep 09

**Subtype** B, C

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade BRU  
*HIV component:* gp160, Rev, Tat

**Species (MHC)** mouse

**Keywords** subtype comparisons, Th1

**References** Arora & Seth 2001

- Plasmid DNA encoding gp160, tat, rev was given i.m. to immunize BALB/c mice.
- Vaccine-induced CTL activity produced a low degree of cell lysis of V3-peptide pulsed target cells, using a B (RGPGRAFTVTI) or C (RIGPGQTFYATG) clade V3 peptides. Th1 proliferative T-cell responses were observed, and weak Ab responses.

**HXB2 Location** gp160 (311–320)

**Author Location** Env (IIIB)

**Epitope** RGPGRAFTVTI

**Epitope name** 10 Env

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* influenza prime with vaccinia boost *Strain:* B clade IIIB *HIV component:* gp160

**Species (MHC)** mouse

**Donor MHC** H-2d

**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$

**Keywords** Th1, Th2, genital and mucosal immunity

**References** Gherardi *et al.* 2003

- Mice were intranasally primed with a recombinant influenza virus A vector that carries HIV-1 Env inserted into its hemagglutinin protein. Boosting was performed intranasally with either influenza-Env or intraperitoneally with two vaccinia virus recombinants expressing the Env protein, VVenv and MVAenv.
- Peritoneal heterologous immunization with VVenv induced a 60-fold higher CD8+ IFN-gamma T cell responses than homologous influenza prime-boost. The intraperitoneal MVAenv boost response was greater than the VVenv boost in

the spleen and genital lymph nodes, while the VVenv response gave the highest boost with the intranasal route.

- Mice with increased CD8+-T-cell responses also had a higher Th1/Th2 ratio, indicated by the cytokine secretion profile and the IgG2a/IgG1 ratio.

**HXB2 Location** gp160 (311–320)

**Author Location** gp160

**Epitope** RGPGRAFTVTI

**Epitope name** P18-I10

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vaccinia with H1 influenza HA gene cassette *Strain:* B clade IIIB *HIV component:* gp160

**Species (MHC)** mouse

**Assay type** Chromium-release assay

**Keywords** genital and mucosal immunity

**References** Kuribayashi *et al.* 2004

- The intraepithelial compartment of the intestinal mucosa is shown to be a major site for preventing virus spread by thymus-derived CD8 $\alpha$  $\beta$ -positive Ag specific CTLs and CD8 $\alpha$ , $\alpha$ + $\gamma$ , $\delta$  cells, which regulate virus spread in a P18-I10 vaccinia vector mouse infection model.

**HXB2 Location** gp160 (311–320)

**Author Location** Env

**Epitope** RGPGRAFTVTI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vesicular stomatitis virus (VSV) *Strain:* B clade *HIV component:* Env

**Species (MHC)** human

**Country** United States

**Assay type** Tetramer binding, Other

**Keywords** memory cells

**References** Ramsburg *et al.* 2007

- The requirement for CD4 T cell help in primary versus memory CTL responses was examined. Since a VSV vector encoding HIV Env was used as vaccine, responses specific to HIV-1 Env epitope RGPGRAFTVTI as well as VSV epitope N were tested. Both primary and memory responses to the Env epitope did not require Th help. However, primary CTL responses to Env were 2-3 fold higher in the presence of CD4 T cells, while memory responses were tested until 3 months post-priming. Thus memory CTL maintenance dependency on CD4 T cell help is epitope-dependent.

**HXB2 Location** gp160 (312–320)

**Author Location** gp120 (V3) (IIIB)

**Epitope** GPGRAFTVTI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* fowlpoxvirus *Strain:* B clade BRVA, B clade IIIB, B clade JY1, B clade LR150, B clade MN, B clade RF *HIV component:* V3

**Species (MHC)** mouse (H-2<sup>d</sup>)



**Keywords** vaccine-specific epitope characteristics, immunodominance

**References** Vázquez Blomquist *et al.* 2002

- BALB/c mice were vaccinated with a polyepitope V3 vaccine in a fowlpoxvirus carrying concatenated 15 mer sections of the V3 loops of HIV-1 isolates LR150, JY1, RF, MN, BRVA and IIIB with 5-aa linkers between, fused to the N-term of p64K protein from *Neisseria meningitidis*.
- Intraperitoneal immunization elicited the strongest V3-specific IFN-gamma response in splenocytes, compared to intravenous and subcutaneous immunization. Intraperitoneal immunization conferred protection in a recombinant vaccinia virus challenge model.
- The immunodominant response was directed against the IIIB peptide (the IIIB immunizing peptide was SIRIQRGP-GRFVFTI, the peptide used to probe the response by Elispot was GPGRFVFTI).
- Low CTL responses were also detected to the LR150 (SRGIRIGPGRAILAT) and RF (RKRTMGPRVYYTT) peptides, no responses were detected to the JY1 (RQSTPIGLGQ-ALYTT), BRVA (RKSITKGPGRVIYAT), or MN (RKRIHIGPGRAFYTT) peptides.

**HXB2 Location** gp160 (312–320)

**Author Location** gp120 (V3)

**Epitope** GPGRFVFTI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost, polyepitope, DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade BRVA, B clade IIIB, B clade JY1, B clade LR150, B clade MN, B clade RF *HIV component:* V3 *Adjuvant:* IFN $\gamma$

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$

**Keywords** Th1

**References** Gómez *et al.* 2004

- Priming of mice with DNA-TAB vector, a polyepitope string carrying 8 different V3 loop sequences, followed by a booster with VV-TAB or MVA-TAB, induced humoral responses, as well as a CD8+ T-cell response against V3 epitopes from three different subtype B HIV isolates. The highest values of specific CD8+ T-cell response were achieved when priming with DNA-TAB and a DNA vector expressing IFN-gamma, followed by a MVA-TAB boost. The T-cell response was Th1.
- The eight V3 loops were linked with an A-G-G-G-A sequence. The three peptides that elicited a response were LR150, SRGIRIGPGRAIL; MN, RKRIHIGPGRAFY; and IIIB, SIRIQRGPGRFVFTI. These peptides were located at the beginning, middle and end of the polyepitope, indicating all parts were able to be processed. It is not known if there is an H-2d epitope in the other five V3 loop variants that did not elicit a response.

**HXB2 Location** gp160 (314–322)

**Author Location** gp120 (312–320)

**Epitope** GRAFVTIGK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*2705)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** Th1, characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of seven patients responded to this peptide with GzB producing cells and with IFN-gamma producing cells.

**HXB2 Location** gp160 (314–322)

**Author Location** gp120 (314–322)

**Epitope** GRAFVTIGK

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B27)

**References** Jardetzky *et al.* 1991

- Study of peptide binding to HLA-B27.

**HXB2 Location** gp160 (321–330)

**Author Location** gp120 (322–330 HIV-MN)

**Epitope** EIIGDIRQAY

**Epitope name** EY10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2501)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Positions 1, 5 and 10 (last) in the epitope had potentially experienced positive selection. qIIGDIRQAY, dIIGDIRQAh, EIIGnIRQAh and EIIGDIRQAh escape variants were found.

**HXB2 Location** gp160 (322–336)

**Author Location** Env

**Epitope** IIGDIRQAHCNISRE

**Subtype** A, B, C, D

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost, protein *Strain:* B clade 1007, B clade 1035 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse

**Country** United States

**Assay type** Cytokine production

**Keywords** subtype comparisons, immunodominance

**References** Brown *et al.* 2006

- A vaccine study with B clade Envs in mice was undertaken to assess a subtype-specificity of responses. Four T-cell hybridomas responsive to subtype B envelope proteins were tested against 20 different subtype B envelope proteins and a protein each from subtypes A, C and D. IL-2 production was measured.
- No consistent correlation was found between T cell specificity towards epitopes from a certain (B) subtype or lack of specificity towards other (A, C, D) subtype.
- Not only did T-cell specificity not vary with subtype, but pairwise sequence comparisons of gp120 envelope sequences showed that some US-derived sequences were more similar to sequences from distant countries than to each other.
- Changes in core epitopes, flanking and distant regions, all affected responsiveness of the hybridomas to different subtype Env epitopes, showing that it is not only core changes that can eliminate T cell reactivity to an epitope.
- The above findings were substantiated by database analyses showing that epitope distributions are not necessarily dictated by subtype.
- This paper lists several variants of the epitope above, IIGDIRQAHCNISRE.

**HXB2 Location** gp160 (337–361)

**Author Location** gp120 (337–368 LAI)

**Epitope** KWNNTLQIDSKLREQFGNNKTIIF

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vaccinia *HIV component:* gp160

**Species (MHC)** human (CD4+ CTL)

**References** Johnson *et al.* 1994a

- CD4+ CTL clones were obtained from an HIV-1 vaccinia-env vaccinee.

**HXB2 Location** gp160 (339–354)

**Author Location** gp120 (339–361 LAI)

**Epitope** NNTLQIDSKLREQFG

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vaccinia *HIV component:* gp160

**Species (MHC)** human (CD4+ CTL)

**References** Johnson *et al.* 1994b

- CD4+ CTL isolated from LAI IIB gp160 vaccinees.

**HXB2 Location** gp160 (340–348)

**Author Location** gp120 (346–354 CM243 subtype CRF01)

**Epitope** RVLKQVTEK

**Epitope name** E340-348

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in HIV+ control study subject 053 who carried HLA-A11.

**HXB2 Location** gp160 (340–348)

**Author Location** gp120 (346–354 CM243 subtype CRF01)

**Epitope** RVLKQVTEK

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This is one of the new A11 epitopes identified through the streamlined EpiMatrix method, and 2/8 tested FSWs recognized it.
- This epitope was not conserved in other subtypes, and exact matches were rare.

**HXB2 Location** gp160 (340–349)

**Author Location** gp120 (W6.ID)

**Epitope** NTLKQIVIKL

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade W61D *HIV component:* gp120

**Species (MHC)** chimpanzee (Patr-B\*14)

**Keywords** immunodominance

**References** Balla-Jhaghoorsingh *et al.* 1999a

- An HIV-1 rgp120 vaccine induced strong humoral and cellular immune response in sibling chimpanzees, but only one of the two made a detectable CTL response to this Patr-B\*14 restricted immunodominant epitope.

**HXB2 Location** gp160 (341–349)

**Author Location** gp120 (341–349 HIV-MN)

**Epitope** TLSQIVTKL

**Epitope name** TL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Position 4 in the epitope had potentially experienced positive selection. T<sub>L</sub>SKIVTKL escape variant was found.

**HXB2 Location** gp160 (344–361)  
**Author Location** gp160 (348–366 WEAU)  
**Epitope** QIVEKLREIKQFKNKTIIVF  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*2902, B\*0801, B\*4403  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** dynamics, immunodominance, escape, kinetics, characterizing CD8+ T cells, viral fitness and reversion

- References** Jones *et al.* 2004
- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
  - The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
  - WEAU had a reaction to an epitope within this peptide, and there was very rapid accumulation of substitutions; variation continued through the last sample collected.

**HXB2 Location** gp160 (363–376)  
**Author Location** (C consensus)  
**Epitope** PSSGGDLEITTHSF  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*18)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** gp160 (369–375)  
**Author Location** gp120 (374–380 BRU)  
**Epitope** PEIVTHS  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

**HXB2 Location** gp160 (374–382)  
**Author Location** Env  
**Epitope** HSFNCGGEF  
**Epitope name** 1325  
**Subtype** multiple  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A02, A03, B08, B51, Cw01, Cw07  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** binding affinity, computational epitope prediction

- References** De Groot *et al.* 2003
- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
  - Estimated binding probability for HSFNCGGEF: 76%

**HXB2 Location** gp160 (375–383)  
**Author Location** gp120 (379–387 LAI)  
**Epitope** SFNCGGEFF  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1516)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1516 epitope.

**HXB2 Location** gp160 (375–383)  
**Author Location** Env  
**Epitope** SFNCGGEFF  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1516)  
**Donor MHC** A\*0202, A\*0301, B\*0702, B\*1516  
**Country** United States  
**Keywords** escape, acute/early infection  
**References** Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- E to G mutation was observed in position 7.

**HXB2 Location** gp160 (375–383)

**Author Location** gp120 (375–383 IIIB)

**Epitope** SFTCGGEFF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- An additional variant that gave a positive, though reduced, CTL response: SSTCGGEFF and SFTCGGGFF.
- SFTCGGGVF was an escape mutant.

**HXB2 Location** gp160 (375–383)

**Author Location** gp120 (375–383 SF2)

**Epitope** SFNCGGEFF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Keywords** HAART, ART, acute/early infection

**References** Altfield *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B15+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 1/1 group 2, and 0/1 group 3.

**HXB2 Location** gp160 (375–383)

**Author Location** gp120 (375–383)

**Epitope** SFNCGGEFF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.

- This is one of 5 epitopes from this individual that varied over time where the internal mutations became fixed; a dramatic decrease in CTL activity against the wild type epitope was observed as the mutation arose. The sfncRgeff variant residue found at 20 and 47 months postseroconversion.

**HXB2 Location** gp160 (375–383)

**Author Location** gp120 (375–383)

**Epitope** SFNCGGEFF

**Immunogen**

**Species (MHC)** (B15, B1516, B63)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 121/200 Brazilian HIV sequences; common variants are tFNCGGEFF and SFNCRGEFF.

**HXB2 Location** gp160 (375–383)

**Author Location**

**Epitope** SFNCGGEFF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B1516, Cw04)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope SFNCGGEFF when restricted by HLA-B1516, elicited a magnitude of response of 765 SFC with a functional avidity of 0.5nM. When restricted by HLA-Cw04, it elicited a magnitude of response of 640 SFC with a functional avidity of 0.5nM.

**HXB2 Location** gp160 (375–383)

**Author Location** gp120

**Epitope** SFNCGGEFF

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B63)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. Borderline significantly more often recognized in subjects who carry B63, but not B57/B58.

**HXB2 Location** gp160 (375–383)**Author Location** gp120 (375–383 IIIB)**Epitope** SFNCGGEFF**Immunogen** HIV-1 infection**Species (MHC)** human (B15, B63)**References** Wilson *et al.* 1997a

- This is the optimal peptide for two CTL clones that recognize this epitope in the context of two different HLA molecules, Cw4 and B15.
- Predominant form in proviral DNA of the individual with B15 restricted CTL was SFTCGGEFF and this was recognized.
- Recognition of a minor autologous variant (SFNCRGEFF) from the B15 donor was greatly reduced.

**HXB2 Location** gp160 (375–383)**Author Location** gp120 (376–383 PV22)**Epitope** SFNCGGEFF**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0401)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a C\*0401 epitope.

**HXB2 Location** gp160 (375–383)**Author Location** gp120**Epitope** SFNCGGEFF**Subtype** A**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0401, Cw\*0407)**Keywords** HIV exposed persistently seronegative (HEPS), cross-presentation by different HLA**References** Bird *et al.* 2002

- 4/123 (2 HIV-1 positive, 2 HEPS) Kenyan female sex workers carried the novel allele HLA Cw\*0407.
- HLA Cw\*0407 did not differ from Cw\*0401 in the region associated with the binding pocket, and Cw\*0407 was shown to cross-present a previously defined Cw\*0401 epitope, SFNCGGEFF (gp120).

**HXB2 Location** gp160 (375–383)**Author Location** gp120 (376–383 PV22)**Epitope** SFNCGGEFF**Immunogen** HIV-1 infection**Species (MHC)** human (Cw4)**References** Johnson *et al.* 1993

- Conserved epitope.

**HXB2 Location** gp160 (375–383)**Author Location** gp120 (376–383 PV22)**Epitope** SFNCGGEFF**Immunogen** HIV-1 infection**Species (MHC)** human (Cw4)**References** Wolinsky *et al.* 1996

- Longitudinal study of epitope variation *in vivo*.

**HXB2 Location** gp160 (375–383)**Author Location** gp120 (376–383)**Epitope** SFNCGGEFF**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human (Cw4)**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-Cw4 women, 1/2 HEPS and 10/11 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 6 of the 10/11 responsive HIV-1 infected women, and not in the HEPS case.

**HXB2 Location** gp160 (375–383)**Author Location****Epitope** SFNCGGEFF**Immunogen** HIV-1 infection, vaccine*Vector/Type:* canarypox prime with gp120 boost *Strain:* Other *HIV component:* gp160**Species (MHC)** human**Donor MHC** A3, A33; B15 (63), B27**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** vaccine-induced epitopes**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.

- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** gp160 (375–384)

**Author Location** (C consensus)

**Epitope** SFNCRGEFFY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*29)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- SFNCRGEFFY is an optimal epitope.

**HXB2 Location** gp160 (375–384)

**Author Location** (B consensus)

**Epitope** SFNCGGEFFY

**Epitope name** SY10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A29)

**Donor MHC** A28, A29, B14, B44, Cw8

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** gp160 (375–384)

**Author Location**

**Epitope** SFNCGGEFFY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A29)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.

- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope SFNCGGEFFY elicited a magnitude of response of 855 SFC with a functional avidity of 0.0001nM.

**HXB2 Location** gp160 (375–384)

**Author Location** gp120 (375–384)

**Epitope** SFNCGGEFFY

**Immunogen**

**Species (MHC)** (A29)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 120/200 Brazilian HIV sequences; common variants are tFNCGGEFFY and SFNCrGEFFY.

**HXB2 Location** gp160 (376–383)

**Author Location** gp120

**Epitope** FNCGGEFF

**Immunogen**

**Species (MHC)** human (Cw4)

**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive,
- HIV-2 sequence: TNCRGEFL – no cross-reactivity Johnson *et al.* [1993]

**HXB2 Location** gp160 (376–383)

**Author Location** gp120 (376–383)

**Epitope** FNCGGEFF

**Immunogen**

**Species (MHC)** (Cw4)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 147/200 Brazilian HIV sequences; a common variant is FNCrGEFF.

**HXB2 Location** gp160 (376–384)

**Author Location** gp120 (376–384 IIIB)

**Epitope** FNCGGEFFY

**Immunogen** HIV-1 infection**Species (MHC)** human (A29)**References** Wilson *et al.* 1997a

- This is the optimal peptide for two CTL clones derived from two different donors.
- FNCRGEFFY and FNCRGGFFY are major and minor autologous variants in one of the donors, and showed reduced or no stimulatory activity for CTL from the host.
- The IIIB form and the form FNCAGEFFY were present in the other donor, and the CTL line had reduced activity with the FNCAGEFFY form relative to the index peptide.

**HXB2 Location** gp160 (376–384)**Author Location** gp120 (376–384 IIIB)**Epitope** PNCGGEFFY**Immunogen** HIV-1 infection**Species (MHC)** human (A29)**Keywords** responses in children, mother-to-infant transmission, escape**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- PNCRGEFFY was an escape variant.

**HXB2 Location** gp160 (376–384)**Author Location** gp120 (376–384 LAI)**Epitope** FNCGGEFFY**Epitope name** E2**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A29)**Keywords** HAART, ART**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** gp160 (376–384)**Author Location** gp120**Epitope** FNCGGEFFY**Immunogen** HIV-1 infection**Species (MHC)** human (A29)**Assay type** Intracellular cytokine staining**Keywords** immunodominance, genital and mucosal immunity**References** Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T cells responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 1/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

**HXB2 Location** gp160 (376–384)**Author Location****Epitope** FNCGGEFFY**Immunogen** HIV-1 infection**Species (MHC)** human (A29)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** binding affinity, immunodominance, optimal epitope**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope FNCGGEFFY elicited a magnitude of response of 80 SFC with a functional avidity of 0.1nM.

**HXB2 Location** gp160 (376–384)**Author Location** gp120 (376–384)**Epitope** FNCGGEFFY**Immunogen****Species (MHC)** (A29)**Keywords** subtype comparisons, viral fitness and reversion**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 145/200 Brazilian HIV sequences; a common variant is FNCrGEFFY.

**HXB2 Location** gp160 (376–384)**Author Location** gp120 (376–384)**Epitope** FNCGGEFFY**Epitope name** FNC**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- One of the 7/8 study subjects that were HLA B8 recognized this CTL epitope.
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSH-FLK, and FNCGGEFFY that declined during therapy initiated at day 197.

**HXB2 Location** gp160 (376–384)

**Author Location** gp160

**Epitope** FNCGGEFFY

**Epitope name** FNC

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** gp160 (376–387)

**Author Location** gp120 (381–392 BRU)

**Epitope** KNCGGEFFYCN

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

**HXB2 Location** gp160 (376–387)

**Author Location** Env (379–)

**Epitope** KNCGGEFFYCN

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A\*0202, A\*0301, B\*0702, B\*1516

**Country** United States

**Keywords** escape, acute/early infection

**References** Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- E to G mutation was observed in position 6.

**HXB2 Location** gp160 (377–386)

**Author Location** gp160 (374–383 SUMA)

**Epitope** NCGGEFFYCN

**Epitope name** gp160 NN10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** gp160 (377–386)

**Author Location** gp120 (377–386)

**Epitope** NCGGEFFYCN

**Immunogen**

**Species (MHC)**

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 135/200 Brazilian HIV sequences; a common variant is NCrGEFFYCN in subtypes C and BF.

**HXB2 Location** gp160 (377–387)

**Author Location** gp120 (377–387)

**Epitope** NSGGEFFYNS

**Immunogen**

**Species (MHC)** human (A2)

**References** Hickling *et al.* 1990

- Peptides recognized by class I restricted CTL can bind to class II.

**HXB2 Location** gp160 (383–391)

**Author Location** gp120 (385–393)



**Epitope** FYCNTTQLF**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2402)**References** Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- FYCNTTQLF bound to A\*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

**HXB2 Location** gp160 (383–391)**Author Location** gp160 (380–389 SUMA)**Epitope** FYCNTTQLF**Epitope name** GP160 FF9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2402)**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** gp160 (404–420)**Author Location** gp120**Epitope** GSNNTVGNPIILPCRI**Subtype** A, B, C, D**Immunogen** vaccine*Vector/Type:* DNA prime with vaccinia boost, protein *Strain:* B clade 1007, B clade 1035**Species (MHC)** human**Assay type** Cytokine production**Keywords** subtype comparisons, immunodominance**References** Brown *et al.* 2006

- A vaccine study with B clade Envs in mice was undertaken to assess a subtype-specificity of responses. Four T-cell hybridomas responsive to subtype B envelope proteins were tested against 20 different subtype B envelope proteins and a protein each from subtypes A, C and D. IL-2 production was measured.
- No consistent correlation was found between T cell specificity towards epitopes from a certain (B) subtype or lack of specificity towards other (A, C, D) subtype.
- Not only did T-cell specificity not vary with subtype, but pairwise sequence comparisons of gp120 envelope sequences showed that some US-derived sequences were more similar to sequences from distant countries than to each other.
- Changes in core epitopes, flanking and distant regions, all affected responsiveness of the hybridomas to different subtype Env epitopes, showing that it is not only core changes that can eliminate T cell reactivity to an epitope.
- The above findings were substantiated by database analyses showing that epitope distributions are not necessarily dictated by subtype.
- This paper lists several variants of the epitope above, GSNNTVGNPIILPCRI.

**HXB2 Location** gp160 (410–429)**Author Location** gp120 (410–429 PV22)**Epitope** GSDTITLPCRIKQFINMWQE**Immunogen** in vitro stimulation or selection**Species (MHC)** human (DRA CD4+)**References** Bouhdoud *et al.* 2000

- CTL were studied through PBMC stimulation *in vitro* by gp120 pulsed autologous monocytes.
- Human CD4+ CTL clone (Een217) is an MHC class II HLA-DRA restricted CTL clone that can lyse antigen presenting HLA-DRA-transfected murine L cells – natural variants of the epitope resulted in an anergic response.
- Low concentrations of the HXB2-derived variant (GSDTITLPCRIKQIINMWQK) induced T cell anergy – higher concentrations could induce proliferation and cytotoxic activity.
- CDC42 (TGDITLPCRIKQII-NRWQV), Eli (TNTNITLQCRKQIIMVAG) and Z3 (CTGNITLPCRIKQIIM-NWQE) variants did not induce proliferation, cytotoxic or anergic responses.

**HXB2 Location** gp160 (416–424)**Author Location** Env (413–421 SF2)**Epitope** LPCRIKQII**Immunogen** HIV-1 infection**Species (MHC)** human (B\*5101)**Keywords** subtype comparisons, rate of progression**References** Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996; Lancet 22:1187, 1986; Hum Immunol 22:73, 1988; Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%

- Of the 172 HIV-1 peptides with HLA-B\*5101 anchor residues, 33 bound to HLA-B\*5101, seven of these peptides were reactive with CTL from 3 B\*5101 positive individuals, and six were properly processed.
- Four of the six epitopes were highly conserved among B subtype sequences, LPCRIKQII is not conserved.

**HXB2 Location** gp160 (416–424)  
**Author Location** gp160 (416–424 LAI)  
**Epitope** LPCRIKQII  
**Subtype** B

**Immunogen**

**Species (MHC)** human (B\*5101)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5101 epitope.

**HXB2 Location** gp160 (416–424)  
**Author Location** gp120 (378–385)  
**Epitope** LPCRIKQII  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (B51)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** gp160 (416–424)  
**Author Location** gp160 (416–429)  
**Epitope** LPCRIKQII  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, escape  
**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** gp160 (416–429)  
**Author Location** gp120 (410–429 H3DCG)  
**Epitope** LPCRIKQFINMWQE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR4 CD4+)  
**References** Siliciano *et al.* 1988

- CD4+ CTL restricted by class II HLA-DR4, targets primed by CD4 mediated uptake of gp120.

**HXB2 Location** gp160 (416–435)  
**Author Location** gp120 (421–440 LAI)  
**Epitope** LPCRIKQFINMWQEVGKAMY  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)

**References** Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

**HXB2 Location** gp160 (419–427)  
**Author Location** gp120 (424–432 HXB2)  
**Epitope** RIKQIINMW  
**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*3201)  
**References** Harrer *et al.* 1996b

- C. Brander notes that this is an A\*3201 epitope in the 1999 database.

**HXB2 Location** gp160 (419–427)  
**Author Location** gp120 (419–427 HXB2)  
**Epitope** RIKQIINMW  
**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*3201)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*3201 epitope.

**HXB2 Location** gp160 (419–427)  
**Author Location** gp120 (419–427)  
**Epitope** RIKQIINMW?

**Immunogen**

**Species (MHC)** human (A29, A32)  
**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was A29 and responded to RIKQIINMW, and another responder was A32 and these are thought to be presenting molecules.
- The sequence is unclear – Betts calls both peptide 30 and peptide 32 gp120 419–427 and the peptide sequences are not provided.

**HXB2 Location** gp160 (419–427)  
**Author Location** gp120 (424–432 LAI)  
**Epitope** RIKQFINMW  
**Subtype** B

**Immunogen**

**Species (MHC)** human (A32)  
**References** Ray *et al.* 1998

- Autologous virus was used to detect CTL in two individuals, and in both cases strain-specific autologous CTL were found.

- The autologous epitope sequence was RIKQIINMW, MN and RF were KIKQFINMW and RIKQFVNMW respectively, and all were reactive with CTL clones.

**HXB2 Location** gp160 (419–427)

**Author Location** gp120 (420–428)

**Epitope** RIKQIINMW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A32)

**References** Ferris *et al.* 1999

- This epitope is processed by a TAP1/2 dependent mechanism.

**HXB2 Location** gp160 (419–427)

**Author Location** gp120

**Epitope** RIKQIINMW

**Epitope name** A32-RW10(gp120)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A32)

**Donor MHC** A32, B44; A30, A32, B18, B27

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient B displayed the greatest response to epitope B44-AW11(p24) and also responded to A32-PW10(RT) in both PB and LN samples, while a third response against epitope A32-RW10(gp120) was only detected in the LN sample. Patient D displayed the greatest response to B27-KK10 (p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

**HXB2 Location** gp160 (419–427)

**Author Location** Env (424–432 BRU)

**Epitope** RIKQIINMW

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A32)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02\_AG-infected Ivorians, and 3/9 B-infected French subjects.

**HXB2 Location** gp160 (421–435)

**Author Location** gp120 (421–440 LAI)

**Epitope** KQFINMWQEVGKAMY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Clerici *et al.* 1991a

- Helper and cytotoxic T cells can be stimulated by this peptide (T1)

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Cease *et al.* 1987

- Helper and cytotoxic T cells can be stimulated by this peptide (T1)

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>a</sup>, H-2<sup>b</sup>, H-2<sup>f</sup>)

**References** Shirai *et al.* 1992

- In a murine system multiple class I molecules can present to CTL.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human

**References** Pinto *et al.* 1995

- CTL and T helper cell reactivity in healthcare workers exposed to HIV.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (MN)

**Epitope** KQIINMWQEVGKAMYA

**Immunogen** HIV-1 infection

**Species (MHC)** chimpanzee

**References** Lubeck *et al.* 1997

- Epitope-specific CTL detected in chimpanzees immunized with adenovirus-HIV-1 MN gp160 recombinant.
- CTL response may account for protection against subsequent HIV-1 SF2 challenge in a chimpanzee lacking neutralizing antibodies.
- Helper and cytotoxic T cells can be stimulated by this peptide (T1)

**HXB2 Location** gp160 (425–434)

**Author Location** Env

**Epitope** NMWQEVGKAM

**Epitope name** 1257

**Subtype** multiple

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A02, A30, B39; A02, A03, B44, Cw05, Cw07

**Country** United States

**Assay type** T-cell Elispot

**Keywords** binding affinity, computational epitope prediction

**References** De Groot *et al.* 2003

- Epitopes defined using sequence parsing and matching algorithm Conservatrix, and epitope prediction tool EpiMatrix, were shown to be conserved in a broad range of HIV-1 sequences derived from different parts of the world. 31 novel highly conserved HIV-1 epitopes were found, among which four were recognized as promiscuous epitopes and five as MHC supertypes.
- Estimated binding probability for NMWQEVGKAM: 50%

**HXB2 Location** gp160 (432–451)

**Author Location** gp120 (439–458 IIIB)

**Epitope** KAMYAPPISGQIRCSSNITG

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP) *HIV component:* CD4BS, Gag, gp120, V3

**Species (MHC)** macaque

**References** Wagner *et al.* 1998b

- A VLP is a non-infectious virus-like particle self-assembled from HIV Pr55 gag – macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains Gag and Env specific CTL were stimulated in each case, and Ab response to gag and gp120 was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4 – despite the CTL and Ab response, immunized macaques were infected by intervenous challenge with SHIV chimeric challenge stock.
- CTL specific for this epitope could be found both before and after SHIV challenge.

**HXB2 Location** gp160 (434–443)

**Author Location** gp120 (431–440)

**Epitope** MYAPPISGQI

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse (H-2K<sup>d</sup>)

**References** Duarte *et al.* 1996

- Tolerization of CTL response with continued administration of soluble peptide.

**HXB2 Location** gp160 (434–448)

**Author Location**

**Epitope** MYAPPISGQIRCSSN

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade *HIV component:* gp140

**Species (MHC)** mouse

**Assay type** proliferation, T-cell Elispot

**References** Kumar *et al.* 2006b

- A recombinant plasmid DNA construct expressing env gp140 from B clade isolate 6101 was developed.
- The construct was highly immunogenic in mice and cross-reacted with clade C peptides. 3 immunodominant peptides were mapped out. Proliferation was observed in CD4+, CD8+ and CCR+ memory T cells.
- Immunodominant peptide MYAPPISGQIRCSSN overlapped with the SYFPEITHI database predicted epitope MYAPPISGQ for the Balb/C mouse H2-Kd loci.

**HXB2 Location** gp160 (435–443)

**Author Location**

**Epitope** YAPPISGQI

**Immunogen** SHIV infection

**Species (MHC)** macaque (Mamu-A\*01)

**References** Egan *et al.* 1999

- SHIV-infected rhesus macaques have high frequencies of response to the SIVmac epitope gag p11C,C-M (CTPYDINQM) but only a fraction of A\*01 monkeys tested have responses to SIVmac pol epitope STPPLVRLV and HIV-1 env epitope YAPPISGQI.

**HXB2 Location** gp160 (435–443)

**Author Location** gp41 (89.6)

**Epitope** YAPPISGQI

**Epitope name** p41A

**Immunogen** SHIV infection, vaccine

*Vector/Type:* DNA, modified vaccinia Ankara (MVA) *Strain:* B clade 89.6, B clade HXBc2 *HIV component:* Env, Gag *Adjuvant:* IL-2/Ig

**Species (MHC)** macaque (Mamu-A\*01)

**Keywords** immunodominance

**References** Barouch *et al.* 2001a

- Mamu-A\*01+ rhesus monkeys infected with SHIV-89.6 and SHIV-HXBc2 make immunodominant responses to SIV Gag p11C epitope (CTPYDINQM) and a subdominant response to HIV-1 Env p41A epitope (YAPPISGQI)
- The binding affinities are the same for the two Mamu A\*01 epitopes, so that is not what dictates the dominance.
- Monkeys vaccinated with MVA vectors carrying SIV gag/pol and HIV-1 env showed the same p11C epitope dominance and p41A epitope subdominance, but co-dominance was observed and the response to p41A increased when DNA vaccination was done using the SIV and HIV genes under CMV promoter control with IL2-IG adjuvant.

**HXB2 Location** gp160 (435–443)  
**Author Location** Env  
**Epitope** YAPPISGQI  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade 89.6P,  
 SIV *HIV component:* Env, Gag  
**Species (MHC)** macaque (Mamu-A\*01)  
**Assay type** Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-specific epitope characteristics, rate  
 of progression, kinetics, memory cells, char-  
 acterizing CD8+ T cells  
**References** Davenport *et al.* 2004

- Activation and expansion of antigen-specific CD8+ T-cells shows a delay following infection that allows early viral replication. Until day 10, the kinetics of CD8+ T-cell expansion was the same in vaccinated and control macaques. An increase in virus-specific CD8+ T-cell numbers around day 10 in vaccinated macaques coincides with a slowing in viral replication. This indicates that while cytotoxic T-lymphocyte-inducing vaccines may have a long-term benefit in controlling viral replication and preventing disease progression, they cannot prevent infection.

**HXB2 Location** gp160 (435–443)  
**Author Location** Env (89.6)  
**Epitope** YAPPISGQI  
**Epitope name** p41A  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade 89.6,  
 SIV *HIV component:* Env, Gag *Adju-  
 vant:* IL-2/Ig  
**Species (MHC)** macaque  
**References** Barouch *et al.* 2000; Shen & Siliciano 2000

- Different HIV strains were used for different regions: SIV-mac239 Gag and HIV-1 89.6P Env
- Monkeys that received the DNA vaccines augmented with IL-2/Ig were infected when challenged with pathogenic SHIV-89.6P, but had potent CTL responses, stable CD4+ T-cell counts, preserved virus-specific CD4+ T-cell responses, low to undetectable viral loads, and no evidence of disease or mortality by day 140 after challenge – monkeys that got a sham vaccine had high viral load, progressed to disease, and were half were dead by day 140.
- IL2/Ig consisting of interleukin-2 (IL-2) for immune stimulation, and the Fc portion of immunoglobulin G (IgG) for stability, was delivered either as protein or as DNA – both enhance the CTL response to vaccination, DNA IL2/Ig giving the most intense response.
- Responses to a dominant Mamu A\*01 gag epitope SIV Gag p11C (CTPYDINQM) and a subdominant epitope HIV-1 Env p41A (YAPPISGQI) were tracked and had good durability prior to challenge, and the higher the prechallenge peak p11C CTL response, the lower the post-challenge viral load.
- No NAb responses were detected in the vaccinated monkeys prior to challenge, and comparable peak NAb titers developed in vaccinated monkeys and control monkeys with preserved CD4+ T-cells.
- Shen *et al.* 2000 is an accompanying commentary.

**HXB2 Location** gp160 (435–443)

**Author Location** Env (89.6)  
**Epitope** YAPPISGQI  
**Epitope name** p41A  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade 89.6,  
 SIV *HIV component:* Env, Gag-Pol *Ad-  
 jutant:* IL-2/Ig  
**Species (MHC)** macaque  
**Keywords** immunodominance  
**References** Barouch *et al.* 2001b

- Different HIV strains were used for different regions: SIV-mac239 Gag/Pol and HIV-1 89.6P Env
- Four monkeys were vaccinated with a modified vaccinia Ankara (MVA) vaccine that elicited strong CTL to the immunodominant SIV gag epitope in 4/4 animals, and 1/4 made a response to the HIV Env epitope YAPPISGQI, as determined by tetramer staining and chromium release assays.
- The animals were infected when challenged with pathogenic SHIV-89.6P, but had potent CTL responses, secondary NAb responses upon challenge, partial preservation of CD4+ T-cell counts, lower viral loads, and no evidence of disease or mortality by day 168 after challenge – monkeys that got a sham vaccine had high viral load, progressed to disease, and 2/4 were dead by day 168.

**HXB2 Location** gp160 (444–453)  
**Author Location** Env  
**Epitope** RCSSNITGLL  
**Immunogen**  
**Species (MHC)** human (B56)  
**References** De Groot *et al.* 2001

- The program Epimatrix was used in conjunction with the program Conservatrix to identify conserved regions of HIV that might serve as epitopes.
- A subset of the potential epitopes was identified that could bind to the appropriate HLA-allele, and 15 of the predicted B7 superfamily (HLA B7, B8, and B58) epitopes were identified that could stimulate IFN $\gamma$  production in an ELISPOT assay.
- RCSSNITGLL was newly defined as an epitope in this study, and was shown to stimulate an ELISPOT response, despite not detectably binding to HLA-B7.

**HXB2 Location** gp160 (460–468)  
**Author Location** Env (173–177)  
**Epitope** YSENSSEYY  
**Subtype** B, C  
**Immunogen** vaccine  
*Vector/Type:* vaccinia, modified vaccinia  
 Ankara (MVA) *HIV component:* Env, Gag,  
 Nef, Pol  
**Species (MHC)** human  
**Country** Switzerland, United States  
**Assay type** Tetramer binding, Flow cytometric T-cell cy-  
 tokine assay, Other  
**Keywords** vaccine-induced epitopes, characterizing  
 CD8+ T cells  
**References** Precopio *et al.* 2007

- Vaccines against vaccinia (MVA or Dryvax) or HIV-1 clade C (NYVAC, a recombinant vaccinia virus) induce a similar polyfunctional CTL profile, secreting IFN-gamma, IL-2, MIP-1beta and TNF-alpha, as well as being CD107a+, CD45RO-CD27intermediate phenotype-polyfunctional CTLs secrete more IFN-gamma than monofunctional CTLs.

**HXB2 Location** gp160 (466–475)

**Author Location** Env (464–473)

**Epitope** EVFRPGGGDM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2601)

**Country** Japan

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay, Other, HLA binding

**Keywords** immunodominance, optimal epitope

**References** Satoh *et al.* 2005

- Reverse immunogenetics was used to identify HIV-1 epitopes presented by HLA-A\*2601. 110 peptides were predicted to bind to HLA-A\*2601. 24 of these were demonstrated to bind through a HLA-A\*2601 stabilization assay. Four of these, including this one, were shown to be epitopes endogenously presented by this allele, that can induce peptide-specific CD8 T-cells. HLA-A\*2601 is common in Asia.
- This epitope was recognized in only 1/7 HLA-A\*2601 HIV infected individuals.

**HXB2 Location** gp160 (478–486)

**Author Location** Env (469–477)

**Epitope** NWRSELYKY

**Subtype** B

**Immunogen** HIV-1 infection, peptide-HLA interaction

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** immunodominance

**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, NWRSELYKY, is similar to human protein peroxysomal acylCoA thioesterase, sequence hNWRSELY.

**HXB2 Location** gp160 (486–494)

**Author Location** gp160 (485–493 SUMA)

**Epitope** YKVVKIEPL

**Epitope name** GP160 YL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, acute/early infection, characterizing CD8+ T cells

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.
- Only four epitopes were found to acquire escape mutations in SUMA over time, and this was one of the 20 that remained invariant. A low level response was detected at acute infection that persisted through early infection.

**HXB2 Location** gp160 (489–508)

**Author Location** gp120 (494–513 BRU)

**Epitope** VKIEPLGVAPTAKRRVVQR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Dadaglio *et al.* 1991

- Defined through blocking CTL activity, and Env deletions.

**HXB2 Location** gp160 (489–508)

**Author Location** Env (501–)

**Epitope** VKIEPLGVAPTAKRRVVQR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A\*0202, A\*0301, B\*0702, B\*1516

**Country** United States

**Keywords** escape, acute/early infection

**References** Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- K to R mutation was observed in position 16.

**HXB2 Location** gp160 (489–508)

**Author Location** Env (496–506 BH10, LAI)

**Epitope** VKIEPLGVAPTAKRRVVQR

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Maksutov *et al.* 2002
- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
  - This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is VAPTKAKRRVV) has similarity with the mast/stem cell growth factor receptor precursor fragment VVPTKADKRRSV.
- HXB2 Location** gp160 (489–508)  
**Author Location** Env (497–512 BH10, LAI)  
**Epitope** VKIEPLGVAPTAKRRVVQR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Maksutov *et al.* 2002
- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
  - This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is APTKAKRRVVQREKRA) has similarity with the human interferon-related IFRD2 (PC4-B) protein fragment ARTKARSVRD-KRA.
- HXB2 Location** gp160 (511–519)  
**Author Location** gp160 (511–519)  
**Epitope** YRLGVGALI  
**Epitope name** YI9  
**Immunogen**  
**Species (MHC)** human (Cw\*18)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is a Cw18 epitope.
- HXB2 Location** gp160 (511–519)  
**Author Location** (C consensus)  
**Epitope** YRLGVGALI  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*1801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - YRLGVGALI is an optimal epitope.
- HXB2 Location** gp160 (511–519)  
**Author Location** gp41 (1–8)  
**Epitope** YRLGVGALI  
**Immunogen** peptide-HLA interaction  
**Species (MHC)** human (Cw\*1801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** optimal epitope

- References** Honeyborne *et al.* 2006
- Novel epitopes are defined for four HLA-alleles common in South African Zulu/Xhosa populations: B\*3910, B\*4201, B\*8101 and Cw\*1801, by motif inference. HLA-A\*2902 was found to overlap those of A1 and A24 supertypes.
  - YRLGVGALI was the optimal epitope for HLA-Cw\*1801 with variants YRLGVGAL, RLGVGALI, YRLGVGALi, dYRLGVGALI having been tested.
- HXB2 Location** gp160 (511–526)  
**Author Location** (C consensus)  
**Epitope** RAVGIGAVFLGFLGAA  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*0801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- HXB2 Location** gp160 (519–543)  
**Author Location** gp41 (519–543)  
**Epitope** FLGFLGAAGSTMGAASLTLTVQARC  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw7)  
**References** Nehete *et al.* 1998a
- Three long-term non-progressors and one asymptomatic HIV+ individual were studied and found to have HLA class I C-restricted CD8+ Env-specific CTLs – Cw7 specific CTL were found against three peptides, including this one.
  - HLA-C antigens are expressed on lymphoid cells to a lesser extent, 10% of either HLA-A or HLA-B.
  - HLA-C confers protection against lysis by natural killer cells and by non-MHC-restricted effector T cells and Cw7 directly governs this resistance to lysis – the authors hypothesize that pathogens that inhibit antigen expression and class I expression may particularly down regulate Cw7, thus triggering non-MHC restricted killing.
- HXB2 Location** gp160 (529–537)  
**Author Location** Env (529–)  
**Epitope** TMGAASITL  
**Epitope name** Env529  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* peptide *HIV component:* gp160 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction  
**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was an intermediate A2 binder that did not induce CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 5/17 HIV+ HLA-A2 subjects.

**HXB2 Location** gp160 (529–537)

**Author Location** gp41 (529–537)

**Epitope** TMGAASITL

**Immunogen**

**Species (MHC)** (A2)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 37/50 Brazilian HIV sequences.

**HXB2 Location** gp160 (548–565)

**Author Location** Env

**Epitope** IVQQSNLLRAIEAQQHL

**Epitope name** ENV-75

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, IVQQSNLLRAIEAQQHL differs from the consensus C sequence IVQQSNLLRAIEAQQHL at 0 amino acid positions, i.e. the two clades' peptides are identical.

**HXB2 Location** gp160 (552–571)

**Author Location** Env (552–571)

**Epitope** QSNLLRAIEAQQHMLQTVW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** gp160 (555–565)

**Author Location** gp41

**Epitope** LLRAIEAQQHL

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11.1)

**Country** Thailand

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** optimal epitope

**References** Kantakamalakul *et al.* 2006

- T cell responses in CRF01\_AE infected individuals from Thailand were studied.
- Based on two overlapping peptide sequences that were both reactive, as well as conserved anchor residues, this peptide is suggested to contain a previously defined epitope, RAIEAQQHL.

**HXB2 Location** gp160 (557–564)

**Author Location** (C consensus)

**Epitope** RAIEAQQM

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RAIEAQQM is an optimal epitope.

**HXB2 Location** gp160 (557–565)

**Author Location** gp41 (557–665)

**Epitope** RAIEAQQWQ

**Epitope name** E3

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5101)

**Keywords** HAART, ART, escape

**References** Samri *et al.* 2000



- The epitope was recognized by patient 246#1 in a study of the effects of therapy escape mutations on CTL recognition.

**HXB2 Location** gp160 (557–565)  
**Author Location** gp41 (46–54 HIV-MN)  
**Epitope** RAIEAQQHL  
**Epitope name** RL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5101)  
**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** optimal epitope  
**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

**HXB2 Location** gp160 (557–565)  
**Author Location** gp41 (46–54)  
**Epitope** RAIEAQQHL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1501, B\*5101, Cw\*0304)  
**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding  
**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism  
**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, RAIEAQQHL, was predicted to be restricted by HLA B\*1501, B\*1517, B\*5101 and C\*0304.

**HXB2 Location** gp160 (557–565)  
**Author Location** gp160 (557–565)  
**Epitope** RAIEAQQHL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B15, B51)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** gp160 (557–565)  
**Author Location** gp41 (557–565 IIIB)  
**Epitope** RAIEAQQHL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**References** Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.
- KAIEAQQHL, a variant found in HIV-1 NY5CG, was also recognized.
- RAIEAQQHM, a variant found in HIV-1 JRC5F, was also recognized.
- RAIDAQQHL, a variant found in HIV-1 ETR, was also recognized.
- RAIKAQQHL, a variant found in HIV-1 CDC42, was also recognized.

**HXB2 Location** gp160 (557–565)  
**Author Location** gp41 (557–565)  
**Epitope** RAIEAQQHL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**References** Ferris *et al.* 1999

- This epitope can be processed by a TAP1/2 dependent mechanism.

**HXB2 Location** gp160 (557–565)  
**Author Location** gp41 (557–565)  
**Epitope** RAIEAQQWQ

**Epitope name** RAI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Keywords** HAART, ART, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.

- None of the 8 study subjects recognized this epitope but none were HLA B51+

**HXB2 Location** gp160 (557–565)

**Author Location** gp41 (47–55)

**Epitope** RAIEAQQHL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** gp160 (557–565)

**Author Location** gp41 (557–565 LAI)

**Epitope** RAIEAQQHL

**Epitope name** E3

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Keywords** HAART, ART

**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** gp160 (557–565)

**Author Location** gp41

**Epitope** RAIEAQQHL

**Epitope name** B51-RL9(qp41)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (557–565)

**Author Location** gp41

**Epitope** RAIEAQQHL

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B58, B63)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. Significantly more often recognized by B63+ and B57/58+ subjects than by negative subjects.

**HXB2 Location** gp160 (557–565)

**Author Location** gp41 (46–54)

**Epitope** RAIEAQQHL

**Epitope name** RL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (C\*03, C\*15)

**Assay type** CTL suppression of replication

**Keywords** class I down-regulation by Nef

**References** Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Env epitope RAIEAQQHL-recognizing HLA-C restricted CTLs were unaffected by Nef.

**HXB2 Location** gp160 (557–565)

**Author Location** gp41 (557–565)

**Epitope** RAIEAQQHL

**Epitope name** RL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*51, Cw\*03)

**Country** Kenya

**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement

**References** McKinnon *et al.* 2007

- The authors suggest that epitope variation has different effects on the HIV- specific immune responses of effector memory T cells (Tem) and central memory T cells (Tcm). They show a lack of correlation between IFN-gamma ELISPOT (Tem typical) and proliferation (Tcm typical) assays for specific epitopes in subjects. Since proliferating CTL also correlate with high intracellular IFN-gamma levels, they surmise that proliferating Tcm differentiate to express Tem functions.
- They also show that proliferating CTL numbers correlate with higher CD4 cell counts.
- Several patients responded strongly to epitope variants that were not part of their autologous HIV-1 sequences. Thus they suggest more comprehensive functional characterizations than the usual overnight IFN-gamma ELISPOTS as well as assessments of Tem versus Tcm specific responses rather than general CTL immune responses.
- 5 variants of this index epitope RAIEAQQHL, RL9, were tested - RAIEAQQHm, RAIEAQQqm, RAIEvQQHL, RAIEgQQHL, RAIEtQQHL. The index peptide RAIEAQQHL and variant RAIEAQQHm while being most prevalent, are commonly recognized in ELISPOT but do not elicit proliferation. Conversely, the relatively rare variant RAIEvQQHL had proliferative responses more often than it was recognized by ELISpot.

**HXB2 Location** gp160 (557–565)  
**Author Location** Env (gp160) (557–565)  
**Epitope** RAIEAQQHL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*0304)  
**Keywords** subtype comparisons  
**References** Currier *et al.* 2002a

- Cross-reactive responses were found in PBMC isolated from individuals infected with either B or CRF01\_AE clade viruses, as determined by Elispot assays of target cells expressing recombinant vaccinia viruses expressing HIV-1 gag, env, nef and pol from many clades.
- CTL from subject US101, infected with a clade B virus, displayed broad cross-reactivity to HIV-1 clade A, B, C, D, CRF01\_AE, F G, recognized this epitope. Clade B and C had a L->M change in the C-term position that was tolerated. The H clade Env was not cross-reactive, and had the sequence RA-IAARQHM.

**HXB2 Location** gp160 (557–565)  
**Author Location** gp41 (46–54)  
**Epitope** RAIEAQQHL  
**Immunogen**  
**Species (MHC)** human (Cw\*0304)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** gp160 (557–565)  
**Author Location** (C consensus)  
**Epitope** RAIEAQQHM  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*0801)  
**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** gp160 (557–565)  
**Author Location** gp160 (557–565)  
**Epitope** RAIEAQQHL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*12)  
**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, RAIEAQQHL, was detected within overlapping peptides IVQQNNLLRAIEAQQHL and LRAIEAQQHLQLTVWGI.

**HXB2 Location** gp160 (557–565)  
**Author Location** gp41 (46–54)  
**Epitope** RAIEAQQHL  
**Immunogen**  
**Species (MHC)** human (Cw\*15)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** gp160 (557–565)  
**Author Location**  
**Epitope** RAIEAQQHL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw03, Cw15)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 2 alleles previously known to be associated (Cw03, Cw15) and 4 additional alleles (A02, A30, B58, Cw04).

**HXB2 Location** gp160 (557–565)

**Author Location**

**Epitope** RAIEAQQHM

**Epitope name** RM9

**Immunogen**

**Species (MHC)** human (Cw8)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a Cw08 epitope.

**HXB2 Location** gp160 (557–565)

**Author Location** gp41 (557–565 IIIB)

**Epitope** RAIEAQQHL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** responses in children, mother-to-infant transmission

**References** Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.
- RAIDAQQHL and RVIEAQQHL, naturally occurring variants, were found in mother and are recognized.

**HXB2 Location** gp160 (557–565)

**Author Location** gp41 (557–565)

**Epitope** RAIEAQQHL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A\*0201, A32, B60, B78, and responded to RAIEAQQHL, previously noted to be B51.

**HXB2 Location** gp160 (557–565)

**Author Location** gp41 (557–565 IIIB)

**Epitope** RAIEAQQHL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** mother-to-infant transmission, escape

**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- This epitope was invariant in both the mother and her infant.

**HXB2 Location** gp160 (557–565)

**Author Location** Env (555–567 BH10, LAI)

**Epitope** RAIEAQQHL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Maksiutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is LL-RAIEAQQHLL) has similarity with human MHC class II regulatory factor RFX1 fragment LLRLMEDQQHMA.

**HXB2 Location** gp160 (557–565)

**Author Location** gp160

**Epitope** RAIEAQQHL

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus  
*HIV component:* Env

**Species (MHC)** human

**Donor MHC** A\*3201, A\*3601, B\*5301, B\*8101, Cw\*0401, Cw\*0804

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

**References** McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than one clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. VTEEFNMWK responses were detected in 2 women that had Env responses to all 4 clades, and clade A gave the highest responses; a VnEEFNMWK variant was in clade B and D, and the clade C Env carried VnEEFNMWK. One woman also reacted with RAIEAQQHL, the other with KNCSFNMTT. RAIEAQQHL was identical in clades A, B, and D, while C carried RAIEAQQHm.

**HXB2 Location** gp160 (557–566)**Author Location** Env (557–566)**Epitope** RAIEAQQHML**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*69, B\*40)**Country** India**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, computational epitope prediction, immunodominance**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef. 3
- of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope RAIEAQQHML had >50% conservation across clades B and non-Indian C, but showed no conservation to subtype A.

**HXB2 Location** gp160 (565–573)**Author Location** Env (565–)**Epitope** LLQLTVWGI**Epitope name** Env565**Immunogen** HIV-1 infection, vaccine*Vector/Type:* peptide *HIV component:* Env  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)**Species (MHC)** human, transgenic mouse (A2)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** binding affinity, subtype comparisons, computational epitope prediction**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CD8+ T-cell IFN gamma responses in mice. Responses to the peptide were not detected in 17 HIV+ HLA-A2 subjects.

**HXB2 Location** gp160 (565–573)**Author Location** gp41 (565–573)**Epitope** LLQLTVWGI**Immunogen****Species (MHC)** (A2)**Keywords** subtype comparisons, viral fitness and reversion**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.

- Present in 26/50 Brazilian HIV sequences; a common variant is mLQLTVWGI in subtypes C and BF.

**HXB2 Location** gp160 (565–573)**Author Location** Env (731–739)**Epitope** LLQLTVWGI**Immunogen** HIV-1 infection**Species (MHC)** human (A2 supertype)**Keywords** supertype, rate of progression**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind four of the five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802).

**HXB2 Location** gp160 (570–589)**Author Location** gp41 (571–590 LAI)**Epitope** VWGIKQLQARILAVERYLKD**Subtype** B**Immunogen** vaccine*Vector/Type:* vaccinia prime with gp160 boost *Strain:* B clade LAI *HIV component:* gp160**Species (MHC)** human (DR-1 CD4+ CTL)**References** Kent *et al.* 1997a

- VWGIKQLQARILAVERYLKD, present in HIV-1 LAI, was the immunizing strain.
- VWGIKQLQARVLAVERYLKD, present in HIV-1 MN, was also recognized.
- VWGIKQPQARVLAVERYLRD was the form carried by the autologous strain that infected the vaccinee.
- Lysis of the target cells by CD4+ CTL was inhibited with the addition of the peptide representing the autologous strain.
- The infecting virus epitope also antagonized the proliferative functions of the CD4+ CTL clone.
- The behavior of the autologous strain presents a possible mechanism for vaccine failure since the infecting virus not only escapes CTL activity, but inhibits the ability of CTL to recognize other variants.

**HXB2 Location** gp160 (572–590)**Author Location** gp41 (572–590 BRU)**Epitope** GIKQLQARILAVERYLKDQ**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* gp160**Species (MHC)** human (DPw4.2)**References** Hammond *et al.* 1991

- CD4+ CTL.

**HXB2 Location** gp160 (575–599)  
**Author Location** gp41 (575–599 IIIB)  
**Epitope** QLQARILAVERYLKDQQLLGIWGCS  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**References** Jassoy *et al.* 1992

- Epitope recognized by CTL clone derived from CSF.

**HXB2 Location** gp160 (577–587)  
**Author Location** (C consensus)  
**Epitope** QTRVLAIERYL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5802)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- QTRVLAIERYL is an optimal epitope.

**HXB2 Location** gp160 (583–592)  
**Author Location** Env  
**Epitope** VERYLKDQQL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)  
**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism  
**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.

- This HLA-B\*14 restricted epitope, VERYLKDQQL was mutated to VERYLrDQQL in the daughter D2 isolate.

**HXB2 Location** gp160 (583–592)  
**Author Location** gp41 (583–592 PV22)  
**Epitope** VERYLKDQQL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**References** Jassoy *et al.* 1993

- HIV-1 specific CTLs release  $\gamma$ -IFN, and  $\alpha$ - and  $\beta$ -TNF.

**HXB2 Location** gp160 (584–592)  
**Author Location** Env  
**Epitope** ERYLKDQQL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)  
**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism  
**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-B\*14/B\*1402 restricted epitope, ERYLKDQQL was mutated to ERYLrDQQL in the daughter D2 isolate.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (584–592 HXB2)  
**Epitope** ERYLKDQQL  
**Epitope name** E4  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A32, B14)  
**Keywords** HAART, ART  
**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.

- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (584–592)

**Epitope** ERYLKDQQL

**Immunogen**

**Species (MHC)** (A32, B14)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 35/50 Brazilian HIV sequences; all variants detected (ERYrKDQQL, ERYgKDQQL, and ERYqKDQQL) involved the same residue.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41

**Epitope** ERYLRDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*14)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2002

- Neisseria gonorrhoea cervicitis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhoea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

**HXB2 Location** gp160 (584–592)

**Author Location** (C consensus)

**Epitope** ERYLKDQQL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*14)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure

imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** gp160 (584–592)

**Author Location** Env (584–592)

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection, in vitro stimulation or selection

**Species (MHC)** human (B\*14)

**Assay type** Other

**Keywords** kinetics

**References** Wick *et al.* 2005

- Experimental and mathematical models were used to estimate the number of HIV-infected cells that can be killed by CD8+ T-cells. On average, CTLs can kill from 0.7 to 3.0 cells/day.
- CTL clones LWC8 and 115M21 recognize epitope ERYLKDQQL and were used to study the inhibition of HIV-1 replication in acutely infected cells in vitro.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (584–592)

**Epitope** ERYLKDQQL

**Epitope name** EL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*32, B\*14)

**Country** Kenya

**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement

**References** McKinnon *et al.* 2007

- The authors suggest that epitope variation has different effects on the HIV- specific immune responses of effector memory T cells (Tem) and central memory T cells (Tcm). They show a lack of correlation between IFN-gamma ELISPOT (Tem typical) and proliferation (Tcm typical) assays for specific epitopes in subjects. Since proliferating CTL also correlate with high intracellular IFN-gamma levels, they surmise that proliferating Tcm differentiate to express Tem functions.
- They also show that proliferating CTL numbers correlate with higher CD4 cell counts.
- Several patients responded strongly to epitope variants that were not part of their autologous HIV-1 sequences. Thus they suggest more comprehensive functional characterizations than the usual overnight IFN-gamma ELISPOTs as well as assessments of Tem versus Tcm specific responses rather than general CTL immune responses.
- 6 variants of this index epitope ERYLKDQQL, EL9, were tested - ERYLqDQQL, EsYLqDQQL, EsYLKDQQL, ERYLrDQQL, ERYLtDQQL, ERYLsDQQL.

**HXB2 Location** gp160 (584–592)

**Author Location** (C consensus)

**Epitope** ERYLKDQQL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1401)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- ERYLKDQQL is an optimal epitope.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (584–592 PV22)

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1402)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1402 epitope.

**HXB2 Location** gp160 (584–592)

**Author Location** gp160 (598–597 BORI, SUMA)

**Epitope** ERYLKDQQL

**Epitope name** gp160 EL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1402)

**Donor MHC** A\*2902, B\*1402, Cw\*0802; A\*1103, A\*2402, B\*1402, B\*1501, Cw\*0802

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, immunodominance, escape, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient BORI had high viral loads and rapid CD4 decline. BORI mounted 8 detected responses. BORI did not control viral replication well, and escape mutations occurred early and in most epitopes, 6/7 that were precisely identified.
- The patient SUMA maintained low viral loads and stable CD4 T cell counts through seven years of follow up. In contrast to more rapid progressors, WEAU and BORI, SUMA a broad response to 24 epitopes, with little immunodominance. Two peptides were somewhat more intensely recognized in acute infection, but this response leveled out early on.

- Eleven variants in the ERYLKDQQL epitope were found in the patient BORI. ERYLKeQQp came up first at day 17 from onset of symptoms, but wasn't tested for escape properties. ERYLrDQQL came up next, by day 31, but didn't confer escape in a Cr release assay. By day 218, three variants were found, all of which gave a diminished response: ERYLrDQQL, ERYLqDQQL, and ERYLsDQQL. By day 556 a complex mixture was present, also including the ERYLmDQQL variant that gave a further reduction in the response, and many double mutants: ERYLmDQrL, ERYLmDrQL, ERYLmDQlL, ERYLrDQrL and ERYrDQrL.
- In SUMA, the only variation found in the 24 epitopes was in three overlapping epitopes in Tat, and in this gp160 epitope; variation accumulated early in infection in the Tat epitopes, but this epitope was stable until a sample 736 days post-infection, when only the ERYLqDQQL variant was detected. This variant was not tested with CTL from SUMA, but gave a diminished response in BORI.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Wagner *et al.* 1998a

- CTL specific for HIV epitopes were used to show that the mediators of both the cytolytic (granzyme A was used as the marker) and non-cytolytic (HIV-1 inhibitory chemokines MIP-1  $\alpha$  and RANTES were used as markers) anti-viral responses are localized within the CTL's cytotoxic granules.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (584–592)

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** HAART, ART

**References** Kalams *et al.* 1999b

- Two patients were followed before and after HAART – reduced plasma HIV-1 RNA levels resulted in a decline in HIV *in vivo* activated specific CTL such that by day 260 CTL activities were undetectable.
- ERYLKDQQL was the dominant response in one of the individuals, SLYNTVATL subdominant.
- Sporadic breakthrough in viremia resulted in increases in CTLp.
- Peptide-tetramer staining demonstrated that declining levels of *in vivo*-activated CTL were associated with a decrease in expression of CD38.
- Memory CTL frequency directed against Vac-Gag, Vac-RT, Vac-Env, and Vac-Nef initially increased with HAART and then decreased with the decline of the viral load.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (591–599 SF2)

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Lieberman *et al.* 1997a



- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A3, -A32, -B7, -B14.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (591–599 SF2)  
**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Keywords** subtype comparisons  
**References** Cao *et al.* 1997a

- The consensus sequence for clades B, C, and D is ERYLKDQQL.
- The consensus sequence for clade A is ERYLRDQQL and it is equally reactive.
- The consensus sequence for clade E is ERYLKDQKF and it is not reactive.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41

**Epitope** ERYLKDQQL  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (B14)  
**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)  
**References** Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A and D subtype consensus are identical to the B clade epitope, ERYLKDQQL.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (584–592)

**Epitope** ERYLKDQQL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**References** Sipsas *et al.* 1997

- HIV IIIB proteins were used to define the range of CTL epitopes recognized by 3 lab workers accidentally infected with HIV-1 IIIB.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (584–592)

**Epitope** ERYLKDQQL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**References** Yang *et al.* 1996

- CD4+ cell lines acutely infected with HIV were studied to determine their susceptibility to lysis by CTL.
- Clones specific for RT lysed HIV-1 infected cells at lower levels than Env or Gag specific clones.
- The distinction was thought to be due to lower expression of RT relative to Env and Gag.

- CTL can lyse infected cells early after infection, possibly prior to viral production.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (584–592)  
**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Assay type** CTL suppression of replication  
**References** Yang *et al.* 1997a

- CTL inhibit HIV-1 replication at effector cell concentrations comparable to those found *in vivo*.
- CTL produced HIV-1-suppressive soluble factors – MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, after antigen-specific activation.
- CTL suppress HIV replication more efficiently in HLA-matched cells.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (584–592 PV22)  
**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**References** Johnson *et al.* 1992

- Two overlapping CTL epitopes were mapped with different HLA restriction (also see YLKDQQLL HLA-B8)

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (584–592 PV22)  
**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**References** Jassoy *et al.* 1993

- HIV-1 specific CTLs release  $\gamma$ -IFN, and  $\alpha$ - and  $\beta$ -TNF.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (584–592 HXB2)  
**Epitope** ERYLKDQQL

**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**References** Kalams *et al.* 1994; Kalams *et al.* 1996

- Longitudinal study of T cell receptor usage in a single individual.
- Persistence of oligoclonal response to this epitope for over 5 years.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (584–592)  
**Epitope** ERYLKDQQL

**Immunogen** peptide-HLA interaction  
**Species (MHC)** human (B14)  
**References** DiBrino *et al.* 1994a

- Epitope studied in the context of HLA-B14 binding.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (584–592)  
**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**References** Hammond *et al.* 1995

- This peptide can be processed for HLA-B14 presentation in a TAP-1/2 independent pathway.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (584–592)

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Kalams *et al.* 1996

- CTL response to this epitope was studied in 5 HLA-B14 positive persons.
- CTL responses were detected in all five, and CTL clones were isolated from 4/5.
- A diverse repertoire of TCRs recognized this epitope, with similar fine specificities.
- 3/5 subjects showed no variation in viral sequence, 2/5 had a dominant variant that resulted in poor recognition, ERYLQDQQL.
- A minor CTL response specific for the ERYLQDQQL could be detected by two individuals, but the major CTL response was to the ERYLKDQQL form even when it was the minority form.
- Some single amino acid substitutions were well tolerated by most of the CTL clones tested, but others, particularly in the center three amino acid positions, abrogated peptide stimulatory activity.

**HXB2 Location** gp160 (584–592)

**Author Location** gp120 (584–592)

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Ferris *et al.* 1999; Hammond *et al.* 1995

- This epitope is processed by both TAP1/2 dependent and independent mechanisms.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41

**Epitope** ERYLKDQQL

**Immunogen**

**Species (MHC)** human (B14)

**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive, and the B35 allele seems to be protective.
- HIV-2 sequence: EKYLQDQAR – no cross-reactivity Johnson *et al.* [1992]

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (SF2)

**Epitope** ERYLKDQQL

**Epitope name** EL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** acute/early infection

**References** Goulder *et al.* 2001a

- Data from patient AC13 suggest a role for this epitope in initial control of viremia in acute infection, as it is one of several subdominant CTL epitopes recognized during the initial decline in viremia.

- A CTL response to SL9, SLYNTVATL, was not evident until 18 months post-presentation.

- Recognized by two A\*0201-positive chronically infected subjects.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (584–592)

**Epitope** ERYLKDQQL

**Epitope name** 588K

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** HAART, ART, TCR usage

**References** Islam *et al.* 2001

- Transcript frequencies of four CTL clones from patient 115, with a chronic and stable HIV-1 infection, were tracked in a longitudinal study of samples collected 6–11 years post infection: clone M21 and E15 recognize ERYLKDQQL, and clone D87 recognizes variant ERYLQDQQL, and clone p175b recognizes the A2 epitope SLYNTVATL.
- CTL clone M21 uses the V $\beta$  4, CDR3 VKDGA, J $\beta$  1.2 TCR beta gene, and clone E15 uses the V $\beta$  4, CDR3 VEDWGGAS J $\beta$  2.1 TCR beta gene, and D87 uses V $\beta$ 8, ALNRVD, J $\beta$ 2.1.
- Responses were stable even through HAART with undetectable viral loads but frequencies varied over time by 100-fold, ranging from 0.012% of the total population for SLYNTVATL at its lowest point to 3.78% for M21, with the relative frequencies of clones shifting over time.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (589–597 SF2)

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B14+ individuals that had a CTL response to this epitope broken down by group: 3/3 group 1, 1/2 group 2, and 0/0 group 3.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (589–597)

**Epitope** ERYLRDQQL

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B14)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (JRCSF)

**Epitope** ERYLKDQQL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Severino *et al.* 2000

- Primary HLA-B14+ CD4+ CD3+ and HLA-mismatched lymphocytes from uninfected donors were infected with JRCSF after isolation then cocultured with the B14-restricted CTL clone 15160/D75 specific for ERYLKDQQL, and viral inhibition was MHC-restricted.
- Primary monocytes and monocyte-derived DC were generated from the same donors, replication of HIV-1 in these cell types was less efficient than in lymphocytes and could also be inhibited by MHC-restricted CTL.
- DC-lymphocyte cluster cultures allowed vigorous viral replication and MHC-restricted CTL viral inhibition was blunted or lost depending on the ratio of DC to CD4+ lymphocyte in the culture.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (SF2)

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.

**HXB2 Location** gp160 (584–592)

**Author Location** Env (589–597)

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** early-expressed proteins, kinetics

**References** Guillon *et al.* 2002b

- An early-expressed Nef protein was modified to contain Env and Pol epitopes to enable the study the effect of expression kinetics on CTL mediated suppression of replication. The "EpiNef" construct was inserted into a recombinant vaccinia virus which was used to infect a target cell line; the target cells were lysed by CTL clones specific for the Env and Pol epitopes indicating that they were properly processed.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41 (584–592)

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Keywords** class I down-regulation by Nef

**References** Yang *et al.* 2002

- Nef down-modulates class I protein expression, and this study demonstrates directly that Nef-deleted HIV-1 NL-43 can be more effectively killed *in vitro* than NL-43 with an intact Nef. The effect was shown to be specific for class I presentation of epitopes, and unlike Nef, deleting Vpr did not alter CTL susceptibility of NL43 infected cells. The CTL clone 15160D75, specific for the class I B14 presented epitope ERYLKDQQL, was one of four used in this study.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41

**Epitope** ERYLKDQQL

**Epitope name** B14-EL9(gp41)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B14)

**Donor MHC** A32, B14, B7

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient A displayed the greatest response to epitope B14-EL9(gp41), a strong response to B7-TL9(p24), and responses to B7-TM9(Nef) and A32-PW10(RT).

**HXB2 Location** gp160 (584–592)

**Author Location** gp41

**Epitope** ERYLKDQQL

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, vaccine

*VectorType:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human (B14)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41 (73–81)  
**Epitope** ERYLKDQQL  
**Epitope name** Env EL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Assay type** Chromium-release assay  
**Keywords** binding affinity, TCR usage, characterizing CD8+ T cells  
**References** Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 4/14 CTL T-cell clones tested were specific for Env EL9. Under conditions of excess peptide (100 $\mu$ g/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 range for Env EL9 was 5,000 - 60,000 pg/ml.

**HXB2 Location** gp160 (584–592)  
**Author Location** (B consensus)  
**Epitope** ERYLKDQQL  
**Epitope name** EL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Donor MHC** A28, A29, B14, B44, Cw8; A25, A32, B08, B14, Cw7, Cw8  
**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN- $\gamma$  and TNF- $\alpha$  exhibit stronger cytotoxic activity than those secreting only IFN- $\gamma$ . These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 2/9 individuals recognized this epitope, presented by HLA-B14.

**HXB2 Location** gp160 (584–592)  
**Author Location** Env (584–592)  
**Epitope** ERYLKDQQL  
**Epitope name** EL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B14)  
**Donor MHC** A\*02, A\*68, B\*14, B\*52, Cw\*08, Cw\*12  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** escape, characterizing CD8+ T cells, optimal epitope

**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The variant ERYLqDQQL was the only form of the epitope detected over a 6-year period in this person. Elispot reactions were reduced to the autologous form relative to the B clade consensus form, ERYLKDQQL.

**HXB2 Location** gp160 (584–592)  
**Author Location** gp41  
**Epitope** ERYLKDQQL  
**Epitope name** EL9  
**Immunogen**  
**Species (MHC)** (B14)  
**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion  
**References** Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** gp160 (584–592)

**Author Location** gp41**Epitope** ERYLKDQQL**Epitope name** B14-EL9(gp41)**Immunogen** HIV-1 infection**Species (MHC)** human (B14)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (584–592)**Author Location****Epitope** ERYLKDQQL**Immunogen** HIV-1 infection, vaccine*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease**Species (MHC)** human (B14)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** gp160 (584–592)**Author Location** gp41 (subtype B)**Epitope** ERYLKDQQL**Subtype** B**Immunogen** HIV-1 exposed seronegative**Species (MHC)** human (B\*1402, B14)**Keywords** subtype comparisons**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.

- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope is ERYLRDQQL.

**HXB2 Location** gp160 (584–592)**Author Location** gp41 (584–592)**Epitope** ERYLKDQQL**Immunogen** HIV-1 infection**Species (MHC)** human**References** Price *et al.* 1995

- Study of cytokines released by HIV-1 specific activated CTL.

**HXB2 Location** gp160 (584–592)**Author Location** gp41 (584–592)**Epitope** ERYLKDQQL**Immunogen** HIV-1 infection**Species (MHC)** human**References** Borrow *et al.* 1994

- Three out of five patients with HIV-1 symptomatic infection controlled their viral infection well and mounted an early, strong HIV-1 specific MHC restricted CTL response.
- One of the three, study subject BORI, specifically recognized this peptide.

**HXB2 Location** gp160 (584–592)**Author Location** gp160**Epitope** ERYLRDQQL**Subtype** A, B, C, D**Immunogen** HIV-1 infection, vaccine*Vector/Type:* vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus *HIV component:* Env**Species (MHC)** human**Donor MHC** A\*0202, A\*7401, B\*1503, B\*5802, Cw\*0202, Cw\*0602; A\*0201, A\*3009, B\*4501, B\*5802, Cw\*0202, Cw\*1601**Country** Kenya**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization**References** McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. ERYLRDQQL responses were detected in 2 women who had Env responses to all 4 clades, and clade A gave the highest responses; a ERYLkDQQL variant was in clade B and

C, and the clade D Env carried ERsLkDQQL. The epitope VS-GFLALAW was also recognized by 1 of the women.

- HLA-B\*5802 was the only HLA common to both women who reacted with ERYLRDQQL, so may be the presenting allele.

**HXB2 Location** gp160 (584–592)

**Author Location**

**Epitope** ERYLKDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0101; B\*0801, B\*1401

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85–86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- ERYLKDQQL was recognized by a placebo patient after infection.

**HXB2 Location** gp160 (584–594)

**Author Location** gp41 (584–594)

**Epitope** ERYLKDQQLLG

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A1A1, B14, B8, Cw7, Cw8

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15–92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** gp160 (584–594)

**Author Location** gp41 (584–594)

**Epitope** ERYLKDQQLG

**Immunogen**

**Species (MHC)**

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 35/50 Brazilian HIV sequences; all variants detected (ERYrKDQQLG, ERYgKDQQLG, and ERYqKDQQLG) involved the same residue.

**HXB2 Location** gp160 (585–592)

**Author Location** gp41 (584–591 SF2)

**Epitope** RYLRDQQL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**References** Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
- This peptide induced CTL in 2/4 HIV-1 + people tested.
- RYLRDQQL bound to A\*2402 weakly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

**HXB2 Location** gp160 (585–592)

**Author Location** gp41 (590–597 LAI)

**Epitope** RYLKDQQL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Shankar *et al.* 1996

**HXB2 Location** gp160 (585–593)

**Author Location** gp41 (585–593)

**Epitope** RYLKDQQLL

**Immunogen**

**Species (MHC)** (A\*23, A24)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 35/50 Brazilian HIV sequences; all variants detected (RYrKDQQLL, RYgKDQQLL, and RYqKDQQLL) involved the same residue.

**HXB2 Location** gp160 (585–593)

**Author Location** gp41 (585–593)

**Epitope** RYLKDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2301)

**Donor MHC** A\*2301, B\*1503, B\*3501, Cw2, Cw7

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** gp160 (585–593)

**Author Location** Env

**Epitope** RYLKDQQLL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2301)

**Donor MHC** A\*2301, A\*6801, B\*5801, B\*5802

**Country** United States

**Keywords** escape, acute/early infection

**References** Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- K to E mutation was observed in position 4.

**HXB2 Location** gp160 (585–593)

**Author Location** gp41 (584–591 SF2)

**Epitope** RYLKDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**References** Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
- This peptide induced CTL in 4/4 HIV-1 + people tested.
- RYLKDQQLL bound to A\*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

**HXB2 Location** gp160 (585–593)

**Author Location** gp41 (591–598 LAI)

**Epitope** RYLKDQQLL

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*2402)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*2402 epitope.

**HXB2 Location** gp160 (585–593)

**Author Location** (C consensus)

**Epitope** RYLKDQQLL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** gp160 (585–593)

**Author Location** Nef

**Epitope** RYLKDQQLL

**Epitope name** RL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** HAART, ART, responses in children, dendritic cells

**References** Zhang *et al.* 2006

- Immune responses in HIV-1 infected children either undergoing HAART or not were analysed. HIV-specific CTLs were lower in children responding to HAART than in non-responders and HAART-naïve children. CTL frequency was correlated with myeloid DC frequency in treatment-naïve patients, and inversely correlated with duration of virus suppression following treatment.
- 11 of the 22 children had significant responses to SL9. USE INA's NOTES

**HXB2 Location** gp160 (585–593)

**Author Location** gp41 (74–82)

**Epitope** RYLKDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A23)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** gp160 (585–593)

**Author Location** gp41

**Epitope** RYLKDQQLL

**Epitope name** A24-RL9(gp41)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A24, B27, B7

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient C displayed the greatest response to B27-KK10(p24), and in decreasing order also responded to A24-RW8(Nef), B7-IL9(gp41), A24-RL9(gp41), A24-YL8(gp41), and B7-TM9(Nef).

**HXB2 Location** gp160 (585–593)

**Author Location** Env

**Epitope** RYLKDQQLL

**Epitope name** RW8

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A2, A24, B38, B60, Cw12, Cw2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, early treatment

**References** Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

**HXB2 Location** gp160 (585–593)

**Author Location** gp41

**Epitope** RYLKDQQLL

**Epitope name** A24-RL9(gp41)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (585–593)

**Author Location**

**Epitope** RYLKDQQLL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (A24)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** gp160 (585–593)

**Author Location**

**Epitope** RYLKDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006



- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope RYLKDQQLL elicited a magnitude of response of 80 SFC with a functional avidity of 5nM.

**HXB2 Location** gp160 (585–593)

**Author Location**

**Epitope** RYLKDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (A24), an additional HLA (A23) was statistically predicted to be associated with this epitope.

**HXB2 Location** gp160 (585–595)

**Author Location** gp41 (584–591 SF2)

**Epitope** RYLKDQQLLGI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**References** Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
- This peptide induced CTL in 4/4 HIV-1 + people tested.
- RYLKDQQLLGI bound to A\*2402 with medium strength, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

**HXB2 Location** gp160 (585–595)

**Author Location** Env (584–594)

**Epitope** RYLKDQQLLGI

**Epitope name** Env584-11

**Immunogen** vaccine

*Vector/Type:* Sendai virus vector system (SeV)

**Species (MHC)** human (A\*2402)

**References** Kawana-Tachikawa *et al.* 2002

- A Sendai virus vector system (SeV) was developed that expressed HLA-A\*2402-restricted class I/peptide complexes; this system could be used to detect responses and has the potential to elicit immune responses.
- MHC class I/peptide tetramers could be made using this system that bound to epitope-specific CTLs in PBMCs.
- Cells transfection with SeV modified to express A\*2402-HIV epitope complexes induced CTL mediated specific cell lysis.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (584–591 NL43)

**Epitope** YLKDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**References** Dai *et al.* 1992

- The lysine (K) is critical for eliciting a HLA-A24 CTL response.
- C. Brander notes that this is an A\*2402 epitope in the 1999 database, and suggested that the epitope is RYLKQQLL.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (591–598)

**Epitope** YLRDQQLL

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A24)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- Variants (R)YL(R/K)DQQLL are specific for the A/B clade.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-A24 women, 3/4 HEPS and 10/10 HIV-1 infected women recognized this epitope, and (R)YL(R/K)DQQLL tended to be reactive in HEPS and infected women, RDYVDRFFKTL in infected women only.
- The dominant response to this HLA allele was to this epitope in all 3/4 HEPS cases but in only 4 of the 10/10 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A\*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (580–587 CM243 subtype CRF01)

**Epitope** YLKDQQLL

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- The only HLA-A24 FSW tested did not recognize the E clade version of this epitope RYLKDKQLL, which differs from the previously defined B clade version by one amino acid, YLKDQQLL, with an additional amino acid added on.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (591–598)

**Epitope** YLKDQQLL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** Th1, characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of seven patients responded to this peptide with GzB producing cells, and a different patient responded with IFN-gamma producing cells.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41

**Epitope** YLKDQQLL

**Epitope name** A24-YL8(gp41)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (586–593)

**Author Location**

**Epitope** YLKDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope YLKDQQLL elicited a magnitude of response of 170 SFC with a functional avidity of 0.005nM.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (586–593 LAI)

**Epitope** YLKDQQLL

**Epitope name** E1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24, B8)

**Keywords** HAART, ART

**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (subtype A)

**Epitope** YLKDQQLL

**Subtype** A

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human, macaque (A24, B8)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (586–593)

**Epitope** YLKDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0801 epitope.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41

**Epitope** YLKDQQLL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Donor MHC** A\*0101, A\*0301, B\*0801, B\*5101; A\*0101, B\*0801

**Country** United Kingdom

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** escape, acute/early infection, variant cross-recognition or cross-neutralization

**References** Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- The second donor in the study shares A\*0101 and B\*0801 with his partner. Escape variant yLQdqql was transmitted, and it reduces binding to B\*0801 by 92% relative to YLKDQQLL.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (586–593)

**Epitope** YLKDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Johnson *et al.* 1992

- Two overlapping CTL epitopes were mapped with different HLA restriction (also see ERYLKDQQL HLA-B14)

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (586–593)

**Epitope** YLKDQQLL

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B8)

**References** Sutton *et al.* 1993

- Predicted epitope based on B8-binding motifs, from larger peptide QLQARILAVERYLKDQQLGIWGCS.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (76–83)

**Epitope** YLKDQQLL

**Immunogen**

**Species (MHC)** human (B8)

**References** Goulder *et al.* 1997g

- Included in a study of the B8 binding motif.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41

**Epitope** YLKDQQLL

**Immunogen**

**Species (MHC)** human (B8)

**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive.
- HIV-2 sequence: YLQDQARL – no cross-reactivity Johnson *et al.* [1992]

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (586–593)

**Epitope** YLKDQQLL

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B8)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** gp160 (586–593)

**Author Location** gp41 (586–593)

**Epitope** YLKDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

**HXB2 Location** gp160 (586–593)

**Author Location** Env (586–593)

**Epitope** YLKDQQLL  
**Epitope name** YL8  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Donor MHC** A\*01, A\*11, B\*08, B\*15, Cw\*04, Cw\*07  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** escape, characterizing CD8+ T cells, optimal epitope  
**References** Koibuchi *et al.* 2005

- HIV-1-specific CD8 T-cell responses were persistent in the chronic phase of HIV-1 infection, although the responses to some of the epitopes declined despite the persistence of the targeted sequences in vivo. Only 4/14 epitopes were potential CTL escape variants, although strong responses to these epitopes persisted for 6 years. This indicates limited viral evolution within targeted CD8 T-cell epitopes during the chronic phase of infection.
- The autologous form of the epitope, YLKDQQLL, matched the B consensus throughout the 5-year period of study, except for 1 rare variant at the first time point, YLrDQQLL, and 1 at year 5, YLKgQQLL.

**HXB2 Location** gp160 (586–593)

**Author Location**

**Epitope** YLKDQQLL

**Immunogen**

**Species (MHC)** (B8)

**Keywords** review, immunodominance, escape, vaccine antigen design

**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

**HXB2 Location** gp160 (586–593)

**Author Location** gp160

**Epitope** YLRDQQLL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML887.

**HXB2 Location** gp160 (586–598)

**Author Location** gp41 (586–598)

**Epitope** YLRDQQLLGIWGC

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw7)

**References** Nehete *et al.* 1998a

- Three long-term non-progressors and one asymptomatic HIV+ individual were studied and found to have HLA class I C-restricted CD8+ Env-specific CTLs – Cw7 specific CTL were found against three peptides, including this one.
- HLA-C antigens are expressed on lymphoid cells to a lesser extent, 10% of either HLA-A or HLA-B.
- HLA-C confers protection against lysis by natural killer cells and by non-MHC-restricted effector T cells and Cw7 directly governs this resistance to lysis – the authors hypothesize that pathogens that inhibit antigen expression and class I expression may particularly down regulate Cw7, thus triggering non-MHC restricted killing.

**HXB2 Location** gp160 (594–608)

**Author Location** gp41

**Epitope** GIWGCSGKLICTTAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Jin *et al.* 1998b

- Progressive HIV-1 infection and CD4 decline was associated decreased the IL-2-expandable HIV-1 CTL response in 10 asymptomatic HIV-infected patients – this observation may be partially due to a reduction and impaired function of T helper cells, CTL exhaustion and APC dysfunction.
- Continued presence of HIV-1 specific memory cells (CTLp) was observed in three patients, one to GIWGCSGKLICTTAV, one to ALIWEDLRSCLFSY, and one to PIPHYCAPAG-FAILKCNNK.

**HXB2 Location** gp160 (594–608)

**Author Location** gp41 (SF2)

**Epitope** GIWGCSGKLICTTAV

**Epitope name** Peptide2

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** Chromium-release assay

**References** Carmichael *et al.* 1996

- Cross-reactivity of Env-specific CTL clones from 14 seropositive HIV-1 infected patients was tested using peptides based on 3 B clade variants (MN, IIB, and RF). The proportion of CTL clones that cross-recognized conserved variants was low. Most CTL clones recognized only one peptide variant, indicating most Env responses are not cross-reactive within the B clade.
- This HLA B17(57) epitope was newly identified within gp41 of HIV-1 SF2. SF2 and IIB have identical sequences within this peptide, but the T-cell clone that recognizes this peptide does not recognize the MN (gFwgcsgklicTtv) or RF (giwgcsklicTtv) variants of this peptide.

**HXB2 Location** gp160 (606–614)

**Author Location** gp41 (605–615 LAI)

**Epitope** TAVPWNASW

- Subtype B**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (MHC)** human (B\*3501)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is a B\*3501 epitope.
- HXB2 Location** gp160 (606–614)  
**Author Location** gp41 (606–614 HXB2)  
**Epitope** TAVPWNASW  
**Subtype B**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**Keywords** epitope processing  
**References** Ferris *et al.* 1996
  - Natural form of this peptide is not glycosylated, suggesting initial Class I processing may occur in the cytosol.

**HXB2 Location** gp160 (606–614)  
**Author Location** gp41 (605–615 LAI)  
**Epitope** TAVPWNASW  
**Subtype B**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (MHC)** human (B35)  
**References** Johnson *et al.* 1994b
  - Epitope for vaccine induced CD8+ clone.

**HXB2 Location** gp160 (606–614)  
**Author Location** gp41 (606–614 LAI)  
**Epitope** TAVPWNASW  
**Subtype B**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (MHC)** human (B35)  
**References** Johnson *et al.* 1994a
  - HLA restricted CTL response to epitope in HIV-1 vaccinia-env vaccinees.

**HXB2 Location** gp160 (606–614)  
**Author Location** gp41 (606–614 LAI)  
**Epitope** TAVPWNASW  
**Subtype B**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (MHC)** human (B35)  
**References** Hammond *et al.* 1995
  - Peptide only processed by a TAP-1/2-dependent pathway.

**HXB2 Location** gp160 (606–614)  
**Author Location** gp41 (606–614)  
**Epitope** TAVPWNASW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**References** Ferris *et al.* 1999

- This epitope is processed by a TAP1/2 dependent mechanism.

- HXB2 Location** gp160 (606–614)  
**Author Location** gp41 (subtype B)  
**Epitope** TAVPWNASW  
**Subtype B**  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (B35)  
**Keywords** subtype comparisons  
**References** Rowland-Jones *et al.* 1998b
- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
  - Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
  - Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
  - This epitope is conserved among A, B and D clade viruses.

- HXB2 Location** gp160 (606–614)  
**Author Location** gp41 (606–614)  
**Epitope** TAVPWNASW  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (B35)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2001a
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

- HXB2 Location** gp160 (606–614)  
**Author Location** gp41 (606–614)  
**Epitope** TAVPWNASW  
**Subtype B**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Donor MHC** A3, A33, B14, B35, Cw\*0401, Cw\*0802  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** binding affinity, acute/early infection, early-expressed proteins  
**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially a showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.

- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** gp160 (606–614)

**Author Location** Env (96–104)

**Epitope** TAVPWNASW

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/9 patients recognized this epitope.

**HXB2 Location** gp160 (614–631)

**Author Location** (C consensus)

**Epitope** WSNKSQEEIWDNMTWMQW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2301)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** gp160 (614–631)

**Author Location** (C consensus)

**Epitope** WSNKSQEEIWDNMTWMQW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0401)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** gp160 (634–648)

**Author Location** gp41 (641–655 SF2)

**Epitope** EIDNYTNTIYTLLEE

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A1, A2, B51, and B57.

**HXB2 Location** gp160 (678–686)

**Author Location** Env (679–687 subtype B)

**Epitope** WLWYIKIFI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity

**References** Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

**HXB2 Location** gp160 (678–686)

**Author Location** Env

**Epitope** WLWYIKIFI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.

- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A2.1 restricted epitope, WLWYIKIFI was the only one mutated, to WLWYIrIFI in the mother M2 isolate.

**HXB2 Location** gp160 (678–686)

**Author Location** gp41 (678–686)

**Epitope** WLWYIKIFI

**Immunogen**

**Species (MHC)** (A2)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 45/50 Brazilian HIV sequences.

**HXB2 Location** gp160 (680–688)

**Author Location** gp41 (679–687 SF2)

**Epitope** WYIKIFIMI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**References** Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
- This peptide induced CTL in 1/4 HIV-1 + people tested.
- WYIKIFIMI bound to A\*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

**HXB2 Location** gp160 (680–688)

**Author Location** gp41 (680–688)

**Epitope** WYIKIFIMI

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2402)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.

- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, WYIKIFIMI, was predicted to be restricted by HLA A\*0203, A\*0206, A\*2402.

**HXB2 Location** gp160 (680–688)

**Author Location** gp41 (680–688)

**Epitope** WYIKIFIMI

**Immunogen**

**Species (MHC)** (A\*2402)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 41/50 Brazilian HIV sequences.

**HXB2 Location** gp160 (681–689)

**Author Location** Env (681–)

**Epitope** YIKIFIMIV

**Epitope name** Env681

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* Env  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a good A2 binder, and induced CTL and CD8+ T-cell IFN gamma responses in mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

**HXB2 Location** gp160 (681–689)

**Author Location** gp41 (681–689)

**Epitope** YIKIFIMIV

**Immunogen**

**Species (MHC)** (A2)

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 41/50 Brazilian HIV sequences.

**HXB2 Location** gp160 (685–693)  
**Author Location** Env (686–694 subtype B)  
**Epitope** FIMIVGGLV  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity

**References** Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.
- ALTERNATIVE EPIPOPE: IMIVGGLVGL – no CTL response was shown to the peptides FIMIVGGLV or IMIVGGLVGL.

**HXB2 Location** gp160 (698–707)

**Author Location** Env (696–706)

**Epitope** VFAVLSIVNR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3303)

**References** Hossain *et al.* 2001; Takiguchi *et al.* 2000

- HLA-A33 a very common allele in Asian, with HLA-A\*3303 the most common among the Japanese. New A\*3303 epitopes were defined to better characterize the immune response in this population.
- The anchor motif for HLA\*3303 (A, I, L, V, F, Y in position 2 (F and Y bind most strongly), and R (K is also tolerated) in the C-terminal position) was used to define 82 potentially reactive peptides in Env; 37/82 peptides bound to A\*3303; 3/37 peptides could induce peptide-specific CTL in bulk PBMC cultures from 1/3 HLA A\*3303 positive individuals tested.
- CTL clones were isolated that killed target cells in a concentration dependent manner after pulsing with the VFAVLSIVNR peptide, that could also kill cells transfected with env expressed from a vaccinia vector. Bulk cultures were tested from six additional people, and only 1/6 reacted with this peptide, but the peptide is in a highly variable region.

**HXB2 Location** gp160 (698–707)

**Author Location** gp41 (187–196)

**Epitope** VFAVLSIVNR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3303)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** gp160 (700–708)

**Author Location** gp41 (705–714)

**Epitope** AVLSVVNRV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Ferris *et al.* 1999

- This epitope is processed by a TAP1/2 dependent mechanism.

**HXB2 Location** gp160 (700–708)

**Author Location** Env (695–705 BH10, LAI)

**Epitope** AVLSVVNRV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Maksutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is LRIVFAVLSVV) has similarity with the human chemokine-factor 3 fragment LRLVFALVTAV .

**HXB2 Location** gp160 (701–719)

**Author Location** Env (691–710)

**Epitope** VLSIVNQVRRQGYSPLSFQT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 5 epitopes from this individual that varied over time where the internal mutations became fixed; a dramatic decrease in CTL activity against the wild type epitope was observed as the mutation arose. The vlsivnKvrrqgysplsfqt variant found at 20 and 47 months postseroconversion.

**HXB2 Location** gp160 (701–720)

**Author Location** gp41 (701–720 BH10)

**Epitope** VLSIVNRVRRQGYSPLSFQTH

**Immunogen** HIV-1 infection

**Species (MHC)** human (A32)

**References** Safrit *et al.* 1994a

- Recognized by CTL derived from acute seroconverter.

**HXB2 Location** gp160 (702–721)

**Author Location** Env (702–721)

**Epitope** LSIVNRVRRQGYSPLSFQTLT

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002



- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** gp160 (703–712)

**Author Location** gp160 (703–712)

**Epitope** EIIIFDIRQAY

**Epitope name** EY10

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a A\*2501 epitope.

**HXB2 Location** gp160 (704–712)

**Author Location** gp160 (704–712 LAI)

**Epitope** IVNRRNRQGY

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*3002)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008; Goulder *et al.* 2001a

- C. Brander notes this is an A\*3002 epitope.

**HXB2 Location** gp160 (704–712)

**Author Location** gp41

**Epitope** IVNRVRQGY

**Epitope name** IY9 (gp41)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*3002)

**References** Goulder *et al.* 2001a

- HLA-A\*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule.
- A rapid method was developed combining ELISPOT with intracellular IFN- $\gamma$  staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood.
- Two individuals were studied: Subject 199 (HLA A\*0201/\*3002 B\*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A\*3002/ B53/\*5801 Cw4/7) an African-Caribbean.
- In both HLA-A\*3002 individuals the response to RSLYNT-VATLY was dominant.
- In subject 199 four additional A\*3002 epitopes were identified.
- Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)

**HXB2 Location** gp160 (704–712)

**Author Location** Env

**Epitope** IVNRRNRQGY

**Epitope name** A30-IY9(env)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A30)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (712–720)

**Author Location** gp41 (201–209)

**Epitope** YSPLSLQTL

**Epitope name** YL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0102)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Last position (9) in the epitope had potentially experienced positive selection. YSPLSLQTr escape variant was found.

**HXB2 Location** gp160 (742–761)

**Author Location** Env (742–761)

**Epitope** RDRSIRLVSGFLALAWDDLRL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.

- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** gp160 (747–755)

**Author Location** gp41 (747–755)

**Epitope** RLVNGSLAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Parker *et al.* 1992

- Studied in the context of HLA-A2 peptide binding.

**HXB2 Location** gp160 (747–755)

**Author Location** gp41 (741–749 CM243 subtype CRF01)

**Epitope** RLVSGFLAL

**Epitope name** E747-755

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was reactive in HIV+ control study subject 144 who carried HLA-A2.

**HXB2 Location** gp160 (747–755)

**Author Location** gp41 (741–749 CM243 subtype CRF01)

**Epitope** RLVSGFLAL

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 2/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by two amino acids, RLVNGSLAL.
- This epitope was somewhat conserved 4/8 subtypes: CRF01 (E), B, C, and G.

**HXB2 Location** gp160 (747–763)

**Author Location** (C consensus)

**Epitope** RLVSGFLALAWDDLRLSL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0202)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** gp160 (749–757)

**Author Location** gp160

**Epitope** VSGFLALAW

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* vaccinia *Strain:* A clade, B clade, D clade NDK, C clade consensus  
*HIV component:* Env

**Species (MHC)** human

**Donor MHC** A\*0202, A\*7401, B\*1503, B\*5802, Cw\*0202, Cw\*0602

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

**References** McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. ERYLRDQQL responses were detected in 2 women who had Env responses to all 4 clades, and clade A gave the highest responses; an ERYLRDQQL variant was in clade B and C, and the clade D Env carried ERsLkDQQL. The epitope VSGFLALAW was also recognized by 1 of the women; A and C clade were identical, while clade B carried VnGsLiLAW, clade D VnGIsAiAW.

**HXB2 Location** gp160 (754–768)

**Author Location** gp41

**Epitope** ALIWEDLRSLCLFSY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B55)

**References** Jin *et al.* 1998b

- Progressive HIV-1 infection and CD4 decline was associated decreased the IL-2-expandable HIV-1 CTL response in 10 asymptomatic HIV-infected patients – this observation may be partially due to a reduction and impaired function of T helper cells, CTL exhaustion and APC dysfunction.
- Continued presence of HIV-1 specific memory cells (CTLp) was observed in three patients, one to GIWGCSGKLICTTAV, one to ALIWEDLRSLCLFSY, and one to PIPIHYCAPAG-FAILKCNNK.

- HXB2 Location** gp160 (754–768)  
**Author Location** gp41 (SF2)  
**Epitope** ALIWERDLRSLCLFSY  
**Epitope name** Peptide78  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B55)  
**Assay type** Chromium-release assay  
**References** Carmichael *et al.* 1996
- Cross-reactivity of Env-specific CTL clones from 14 seropositive HIV-1 infected patients was tested using peptides based on 3 B clade variants (MN, IIIB, and RF). The proportion of CTL clones that cross-recognized conserved variants was low. Most CTL clones recognized only one peptide variant, indicating most Env responses are not cross-reactive within the B clade.
  - This HLA B22(55) epitope was defined using SF2 peptides. The CTL clone that recognized it did not cross-recognize the MN, IIIB, or RF variants of this peptide.

- HXB2 Location** gp160 (754–768)  
**Author Location** gp41 (761–775)  
**Epitope** ALIWEDLRSLCLFSY  
**Epitope name** Peptide 701.78  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B55)  
**Donor MHC** A11, A24, B44, B55  
**Country** United Kingdom  
**Assay type** Flow cytometric T-cell cytokine assay, Other  
**Keywords** HAART, ART, immunodominance, TCR usage, memory cells  
**References** Weekes *et al.* 2006
- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintenance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

- HXB2 Location** gp160 (760–767)  
**Author Location** gp41 (760–767)  
**Epitope** LRSLFLFS  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2301)  
**Donor MHC** A\*2301, B\*1503, B\*3501, Cw2, Cw7  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** binding affinity, acute/early infection, early-expressed proteins  
**References** Cao *et al.* 2003
- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later

- in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
  - More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

- HXB2 Location** gp160 (767–775)  
**Author Location** gp41 (766–774 SF2)  
**Epitope** SYRRLRDLL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2402)  
**References** Ikeda-Moore *et al.* 1997
- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
  - This peptide induced CTL in 1/4 HIV-1 + people tested.
  - SYRRLRDLL bound to A\*2402 moderately, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

- HXB2 Location** gp160 (767–775)  
**Author Location** gp41  
**Epitope** SYHRLRDFI  
**Epitope name** E  
**Subtype** A  
**Immunogen** vaccine  
**Vector/Type:** DNA with CMV promoter, modified vaccinia Ankara (MVA), DNA prime with modified vaccinia Ankara (MVA) boost **Strain:** A clade **HIV component:** Env, Gag, Nef, RT  
**Species (MHC)** mouse (H-2K<sup>d</sup>)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** subtype comparisons, vaccine-induced epitopes, variant cross-recognition or cross-neutralization, antagonism  
**References** Larke *et al.* 2007
- Cross-clade vaccine recognition was studied using either single-, multi or several anatomically separated single-clade vaccines. Limited cross-clade response was seen with single-clade administrations. Multi-clade vaccines gave immune interference (antagonism and original antigenic sin), reducing CTL response. Simultaneously administered but anatomically separated vaccines from clades A, B, C decreased antagonism and increased immune responses.

- After immunization with Clade A vaccine containing Epitope E, SYHRLRDFI, T cells were able to respond to epitope variant SYHRLRDFv, as well as variants SYHRLRDci, SYHRLRDii and SYHRLRDli at <50% magnitude. Variants SYrhLRDFI, iYHhLRDii and SYrhLRDii were not recognized.

**HXB2 Location** gp160 (767–780)  
**Author Location** gp41 (606–614 LAI)  
**Epitope** SYHRLRDLLIVTR  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (A31)  
**References** Hammond *et al.* 1995
- Peptide only processed by a TAP-1/2-dependent pathway.
  - CTL from an acute seroconverter.

**HXB2 Location** gp160 (769–777)  
**Author Location** gp41 (769–777 BH10)  
**Epitope** HRLRDLLLI

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Safrit *et al.* 1994a
- Recognized by CTL derived from acute seroconverter.

**HXB2 Location** gp160 (770–778)  
**Author Location** Env (679–777)  
**Epitope** RLRDLLLIV

- Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** binding affinity  
**References** Kmiecik *et al.* 1998a
- CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL – all have A2 anchor residues.
  - The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*.
  - Peptides 5.3 and D2 bound to HLA A\*0201 with low affinity.

**HXB2 Location** gp160 (770–780)  
**Author Location** gp41 (768–778 NL43)  
**Epitope** RLRDLLLIVTR

- Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**References** Takahashi *et al.* 1991
- CD8+ T cell clone.

**HXB2 Location** gp160 (770–780)  
**Author Location** gp41 (775–785 LAI)  
**Epitope** RLRDLLLIVTR  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is an A\*0301 epitope.

**HXB2 Location** gp160 (770–780)

**Author Location** gp41 (770–780 BH10)

**Epitope** RLRDLLLIVTR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3101)

- References** Safrit *et al.* 1994a; Safrit *et al.* 1994b
- Recognized by CTL derived from acute seroconverter.
  - C. Brander notes that this is an A\*3101 epitope in the 1999 database.

**HXB2 Location** gp160 (770–780)  
**Author Location** gp160 (770–780 LAI)  
**Epitope** RLRDLLLIVTR  
**Subtype** B

- Immunogen**  
**Species (MHC)** human (A\*3101)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- C. Brander notes this is an A\*3002 epitope.

**HXB2 Location** gp160 (770–780)  
**Author Location**  
**Epitope** RLRDLLLIVTR

- Immunogen** HIV-1 infection  
**Species (MHC)** human (A03, A31)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, immunodominance, optimal epitope  
**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope RLRDLLLIVTR when restricted by HLA-A03 elicited a magnitude of response of 450 SFC with a functional avidity of 0.5nM and binding affinity of 9.6nM. When restricted by HLA-A31, it elicited a magnitude of response of 450 SFC with a functional avidity of 0.05nM and binding affinity of 3.8nM.

**HXB2 Location** gp160 (770–780)  
**Author Location**

**Epitope** RLRDLLLIVTR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A03, A31)

- Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** supertype, cross-presentation by different HLA  
**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 2 alleles previously known to be associated (A03, A31) and 4 additional alleles (A02, A74, B44, Cw04).

**HXB2 Location** gp160 (770–780)

**Author Location** gp41 (768–778 NL43)

**Epitope** RLRDLLLIVTR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** subtype comparisons

**References** Cao *et al.* 1997a

- The consensus peptide of clade B is RLRDLLLIVTR.
- The consensus peptide of clades A, C and E is RLRDFILIVTR and it is less reactive.
- The consensus peptide of clade D is SLRDLLLIVTR and it is less reactive.

**HXB2 Location** gp160 (770–780)

**Author Location** gp41 (775–785)

**Epitope** RLRDLLLIVTR

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A3)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** gp160 (770–780)

**Author Location** gp41 (770–780)

**Epitope** RLRDLLLIVTR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.

**HXB2 Location** gp160 (770–780)

**Author Location** Nef (73–82)

**Epitope** RLRDLLLIVTR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- All patients recognized at least 1 A3 epitope, up to 8 A3 epitopes, but none was clearly dominant.
- In two of the subjects, RLRDLLLIVTR was the dominant epitope.

**HXB2 Location** gp160 (770–780)

**Author Location** gp41 (769–780)

**Epitope** RLRDLLLIVTR

**Epitope name** A3-RR11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals began to have detectable responses to this epitope after STI.

**HXB2 Location** gp160 (770–780)

**Author Location** Env (770–780)

**Epitope** RLRDLLLIVTR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. rlrldllivtr variant residues were found. The V mutation arose at late time points, the I mutation arose at intermediate time points.

**HXB2 Location** gp160 (770–780)

**Author Location** Env (786–778)

**Epitope** RLRDLLLIVTR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 14 patients recognized this epitope.

**HXB2 Location** gp160 (770–780)

**Author Location** gp41 (770–780)

**Epitope** RLRDLLLIVTR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A31)

**References** Ferris *et al.* 1999; Hammond *et al.* 1995

- This epitope is processed by a TAP1/2 dependent mechanism.

**HXB2 Location** gp160 (770–780)

**Author Location** gp41 (770–780)

**Epitope** RLRDLLLIVTR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A31)

**Donor MHC** A\*0201, A31, B44, B60, Cw16, Cw3

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.

- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes was characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** gp160 (770–780)

**Author Location** Env

**Epitope** RLRDLLLIVTR

**Epitope name** TW10

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A31)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** epitope processing, escape

**References** Draenert *et al.* 2004b

- This study characterizes the N-terminal flanking position of the epitope ISPRTLNAW, and mutations in this position are thought to impact processing. The A31 epitope RLRDLLLIVTR was used as a negative control in this study.

**HXB2 Location** gp160 (770–780)

**Author Location** gp41 (775–785)

**Epitope** RLRDLLLIVTR

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for IFN $\gamma$  responses to other epitopes.
- 1/11 of the HLA A2+ was HLA A\*0201, A31, B8, B51 and responded to this epitope that has been previously noted to be HLA A3.1, as well as seven others.

**HXB2 Location** gp160 (777–785)

**Author Location** gp41 (782–790 LAI)

**Epitope** IVTRIVELL

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*6802)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*6802 epitope.

**HXB2 Location** gp160 (781–795)

**Author Location**

**Epitope** IVELLGRRGWEVLKY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0101; B\*0801, B\*1401

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- IVELLGRRGWEVLKY was recognized by a placebo patient after infection.

**HXB2 Location** gp160 (781–802)

**Author Location** gp41 (788–809 HXB2)

**Epitope** IVELLGRRGWEALKYWVWLLQY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Lieberman *et al.* 1992

- CTL epitope defined by T cell line and peptide mapping.

**HXB2 Location** gp160 (781–802)

**Author Location** gp120 (788–809)

**Epitope** IVELLGRRGWEALKYWVWLLQY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** gp160 (786–794)

**Author Location** gp41 (751–759)

**Epitope** GRRGWEALK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*2705)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** Th1, characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- One of seven patients responded to this peptide with GzB producing cells, and a different patient responded with IFN-gamma producing cells.

**HXB2 Location** gp160 (786–794)

**Author Location** gp41 (791–799 LAI)

**Epitope** GRRGWEALK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Keywords** review

**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.
- Also: J. Liebermann 1992 and pers. comm. J. Liebermann.

**HXB2 Location** gp160 (786–795)

**Author Location** gp41 (791–800 LAI)

**Epitope** GRRGWEALKY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*2705)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*2705 epitope.

**HXB2 Location** gp160 (786–795)

**Author Location** gp41 (791–800 LAI)

**Epitope** GRRGWEALKY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Lieberman 1998

- Optimal peptide mapped by titration J. Lieberman, pers. comm.

**HXB2 Location** gp160 (786–795)

**Author Location** gp41 (786–795)

**Epitope** GRRGWEALKY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Day *et al.* 2001

**HXB2 Location** gp160 (786–795)

**Author Location**

**Epitope** GRRGWEALKY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B2705)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope GRRGWEALKY elicited a magnitude of response of 215 SFC with a functional avidity of 5nM.

**HXB2 Location** gp160 (787–795)

**Author Location** gp160 (787–795)

**Epitope** RRGWEVLKY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0101)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** gp160 (787–795)  
**Author Location** gp41 (787–795)  
**Epitope** RRGWEVLKY

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A1)  
**Donor MHC** A1A1, B14, B8, Cw7, Cw8  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** binding affinity, acute/early infection, early-expressed proteins  
**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes was characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** gp160 (787–795)  
**Author Location** gp41  
**Epitope** RRGWEVLKY

**Epitope name** A1-RY9(gp41)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A1)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules was studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).

- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (787–795)  
**Author Location**  
**Epitope** RRGWEVLKY

**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human  
**Donor MHC** A1, A2; B38, B8  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes  
**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** gp160 (787–805)  
**Author Location** (C consensus)  
**Epitope** QRGWEALKYLGSLVQYWGL  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*2301)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.

**HXB2 Location** gp160 (794–802)  
**Author Location** gp160 (794–802 LAI)  
**Epitope** KYCWNLLQY  
**Subtype** B

**Immunogen**  
**Species (MHC)** human (A\*3002)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008; Goulder *et al.* 2001a  
 • C. Brander notes this is an A\*3002 epitope.

**HXB2 Location** gp160 (794–802)  
**Author Location** gp41  
**Epitope** KYCWNLLQY



- Epitope name** KY9 (gp41)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3002)  
**References** Goulder *et al.* 2001a
- HLA-A\*3002 is very common in African populations, 50% of Zimbabweans express HLA-A30, 44% in African Zulu, so five new HIV epitopes were characterized that are presented by this HLA molecule.
  - A rapid method was developed combining ELISPOT with intracellular IFN- $\gamma$  staining of PBMCs to map optimal epitopes, then HLA presenting molecules were defined – this method was completed within 48 to 72 hours of receipt of blood.
  - Two individuals were studied: Subject 199 (HLA A\*0201/\*3002 B\*4402/51 Cw2/5), a Caucasian, and Subject 6007 (HLA A\*3002/ B53/\*5801 Cw4/7) an African-Caribbean.
  - In both HLA-A\*3002 individuals the response to RSLYNT-VATLY was dominant.
  - In subject 199 four additional A\*3002 epitopes were identified.
  - Three quantitative assays, ELISPOT, precursor frequency and chromium release, confirmed a hierarchy of response: RY11 (p17) > KY9 (gp41) > KY9 (RT-53) > IY9 (gp41)

**HXB2 Location** gp160 (794–802)  
**Author Location** gp41 (283–291)  
**Epitope** KYCWLLQY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3002)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** gp160 (794–802)  
**Author Location**  
**Epitope** KYCWLLQY?  
**Epitope name** KIY9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3002)  
**Country** United States, South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding  
**Keywords** memory cells  
**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** gp160 (794–802)  
**Author Location** Env  
**Epitope** KYCWLLQY  
**Epitope name** A30-KQY9(env)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A30)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (794–814)  
**Author Location** gp41 (SF2)  
**Epitope** KYCWLLQYWSQELKNSAVSL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human

- References** Altfeld *et al.* 2000
- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
  - The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

**HXB2 Location** gp160 (795–816)  
**Author Location** gp41 (802–823 HXB2)  
**Epitope** YWVLLQYWSQELKNSAVNLLN  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1992
- CTL epitope defined by T cell line and peptide mapping.

**HXB2 Location** gp160 (799–807)  
**Author Location** Env (800–808 subtype B)  
**Epitope** LLQYWSQEL  
**Subtype** B  
**Immunogen** vaccine  
**Vector/Type:** protein **Strain:** B clade MN  
**HIV component:** gp160

- Species (MHC)** human (A\*0201)  
**Keywords** binding affinity  
**References** Kundu *et al.* 1998a
- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
  - Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
  - Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.

- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

**HXB2 Location** gp160 (805–814)  
**Author Location** gp41 (810–819 LAI)  
**Epitope** QELKNSAVSL  
**Subtype** B

**Immunogen**  
**Species (MHC)** human (B\*4001)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*4001,B60 epitope.

**HXB2 Location** gp160 (805–814)  
**Author Location** Env (805–814)  
**Epitope** QELKNSAVSL

**Epitope name** QL10  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4001)  
**Donor MHC** A\*0201, A\*2402, B\*4001, B\*5001, Cw03, Cw04

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization  
**References** Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, QELKNSAVSL (QL10) was restricted by HLA-B\*4001. A variant that arose was QELKkSAVSL.

**HXB2 Location** gp160 (805–814)  
**Author Location** gp41 (SF2)  
**Epitope** QELKNSAVSL

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B60)  
**References** Altfield *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes.
- B60 is present in 10-20% of the Caucasoid and very common in Asian populations.

**HXB2 Location** gp160 (805–814)  
**Author Location** gp41 (805–814)  
**Epitope** QELKNSAVSL

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B60, B61)  
**Keywords** immunodominance  
**References** Day *et al.* 2001

- No immunodominant responses were detected to five B61-restricted epitopes tested.
- All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response.

**HXB2 Location** gp160 (805–814)  
**Author Location** Env (799–813 BH10, LAI)  
**Epitope** QELKNSAVSL

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Maksutov *et al.* 2002

- This study employs an antigenic similarity matrix to compare HIV-1 antigenic determinants with human proteins.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is LLQY-WSQELKNSAVS) has similarity with the complement component C6 fragment LTQFSSEELKNSGLT.
- This CTL epitope (the HIV-1 LAI fragment with high similarity to a human protein overlapping this epitope is NSAVSLL-NATAIAYA) also has similarity with the human INT-2 proto-oncogene protein precursor (fibroblast growth factor-3) fragment NSAYSILEITAVEVG.

**HXB2 Location** gp160 (813–822)  
**Author Location** Env (813–822)  
**Epitope** SLLNATAIAV  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** United States  
**Assay type** Intracellular cytokine staining, Other  
**Keywords** rate of progression, escape, immune evasion  
**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- Responses to epitope SLLNATAIAV were seen in early chronic infection. This was one of the epitopes targeted by broad HLA-A2-restricted CTL responses.

**HXB2 Location** gp160 (813–822)  
**Author Location** gp41 (814–823 LAI)  
**Epitope** SLLNATDIAV  
**Subtype** B  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160

**Species (MHC)** human (A\*0201)

**References** Dupuis *et al.* 1995

- Of two CTL clones, one reacted only with 815-823, the other with 814-823 and 815-823.
- Noted to be A\*0201 in Brander *et al.*, 1999 database.

**HXB2 Location** gp160 (813–822)

**Author Location** Env (814–823 subtype B)

**Epitope** SLLNATDIAV

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity

**References** Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – only individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.
- CTL to overlapping peptides in this region gave a positive response in the greatest number of patients.
- ALTERNATIVE EPITOPES: LLNATDIAV and LLNATDIAVA – CTL were induced by vaccine in those that had the sequence SLLNATAIAVA in their own infection, but not in those with: NLLNTIAIAVA or NLFNTTIAIAVA or SLLNATAITVA.

**HXB2 Location** gp160 (813–822)

**Author Location** gp41 (818–827 LAI)

**Epitope** SLLNATDIAV

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160

**Species (MHC)** human (A\*0201)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0201 epitope.

**HXB2 Location** gp160 (813–822)

**Author Location** gp41 (814–823 LAI)

**Epitope** SLLNATDIAV

**Epitope name** LR27

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade LAI  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 720), P30, PLG

**Species (MHC)** mouse (A\*0201)

**Keywords** binding affinity, vaccine-specific epitope characteristics, immunodominance

**References** Peter *et al.* 2001

- The stability of peptide binding to HLA-A2.1 was determined for six HLA-A2.1 peptides included in this vaccine study – ILKEPVHGV (RT), SLYNTVATL (p17), SLLNATDIAV (gp41) and LLWKGEAV (RT) all bound with high affinity comparable to a influenza epitope reference (GILGFVFTL), while RGPGRAFVTI and VIYQYMDDL bound with a lower affinity (relative binding activity = 0.01).
- The four high-affinity peptides formed stable complexes with half-lives ranging between 8 and 32 hours, while the low affinity peptides had half lives of less than an hour.
- HLA-A2.1 transgenic mice were immunized with the six HIV-1 peptides and P30, as a universal T-helper epitope, with IFA or Montanide or microspheres as adjuvants.
- All peptides except VIYQYMDDL induced a strong CTL response in Cr-release assays - stronger responses were observed when peptides were delivered alone, indicating immunodominance when the combination was used.

**HXB2 Location** gp160 (813–822)

**Author Location** gp41 (814–823 LAI)

**Epitope** SLLNATDIAV

**Epitope name** LR27

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade LAI  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12, P30

**Species (MHC)** mouse (A\*0201)

**Keywords** vaccine-specific epitope characteristics, immunodominance

**References** Peter *et al.* 2002

- When HIV-1 peptides were used to vaccinate HLA-A2.1 transgenic A2-Kb mice, strong responses to five peptides were observed when the peptides were given individually, but immunodominance limited the response to some of the peptides when they were given in combination Peter *et al.* [2001]. IL-12 can counteract immunodominance in BALB/c mice, so it was given with the multiple epitope vaccination, and was instead found to specifically eliminate the HLA-A2.1-epitope CTL responses, but not Kb CTL responses. This was possibly a consequence of transient depletion of T-cells, B cells and macrophages in the spleen.

**HXB2 Location** gp160 (813–822)

**Author Location** gp41 (814–823)

**Epitope** SLLNATDIAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** dendritic cells

**References** Kundu *et al.* 1998b

- Allogeneic dendritic cells (DCs) were obtained from HLA-identical siblings, pulsed with rgp160 MN or A2-restricted HIV-1 epitope peptides, and infused monthly into six HIV-infected patients.

- 1/6 showed increased env-specific CTL and increased lymphoproliferative responses, 2/6 showed increase only in proliferative responses, and 3/6 showed no change – pulsed DCs were well tolerated.
- SLLNATDIAV is a conserved HLA-A2 epitope included in this study – 4/6 patients had this sequence as their HIV direct sequence, and 3 of these had a detectable CTL response – the other two had either the sequence SLFNAIDIAV or SLLNTTDIVV and no detectable CTL response.
- CTL demonstrated against peptide-coated target, epitope is naturally processed and enhancible with vaccine.

**HXB2 Location** gp160 (813–822)

**Author Location** gp41 (818–827)

**Epitope** SLLNATDIAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes, including this epitope.

**HXB2 Location** gp160 (813–822)

**Author Location** gp41 (SF2)

**Epitope** SLLNATAIAV

**Epitope name** SV10

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** acute/early infection

**References** Goulder *et al.* 2001a

- Dominant CTL epitope in acute infection of patient AC13–response to this epitope corresponded to reduction of initial viremia.
- Several other subdominant CTL epitopes were identified in the acute phase, but a response to SL9, SLYNTVATL, was not evident until 18 months post-presentation.

**HXB2 Location** gp160 (813–822)

**Author Location** gp41 (77–85 SF2)

**Epitope** SLLNATDIAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic

infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.

- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 1/10 group 1, 2/6 group 2, and 1/4 group 3.

**HXB2 Location** gp160 (813–822)

**Author Location** gp41 (814–823 CM243 subtype CRF01)

**Epitope** SLLNATAIAV

**Epitope name** E813-82

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was reactive in HIV+ control study subjects 125 and 144 who carried HLA-A2.

**HXB2 Location** gp160 (813–822)

**Author Location** gp41 (814–823 CM243)

**Epitope** SLLNATAIAV

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by one amino acid, SLLNATDIAV.
- This epitope was somewhat conserved 4/8 subtypes: CRF01 (E), B, D, and F.

**HXB2 Location** gp160 (813–822)

**Author Location** gp41 (813–822)

**Epitope** SLLNATDIAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)

- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

**HXB2 Location** gp160 (813–822)  
**Author Location** gp41 (813–822 IIIB)  
**Epitope** SLLNATAIAV  
**Epitope name** D2  
**Subtype** B  
**Immunogen** vaccine

*Vector/Type:* DNA, DNA with protein boost  
*Strain:* B clade IIIB *HIV component:*  
 gp160, gp160ΔV3 *Adjuvant:* IL-12

**Species (MHC)** mouse (A2)  
**Keywords** vaccine-specific epitope characteristics  
**References** Kiszka *et al.* 2002

- Transgenic mice expressing a HLA-A2/Kb chimeric protein were vaccinated with a full length gp160 or with gp160deltaV3, with the V3 loop deleted. Mice given gp160deltaV3 had a broader immune response than those given gp160, with increased responses to conserved HLA-A2 epitopes in the C1 region of gp120, KLTPLCVTL, and the C-term region of gp41, SLLNATAIAV.
- Greater resistance was conferred by the gp160deltaV3 than the gp160 vaccine to a challenge of vaccinia expressing heterologous gp160 from primary isolates (VI-06 and 89.6), and the resistance was conferred by CD8+ T-cells.

**HXB2 Location** gp160 (813–822)  
**Author Location** Env (813–)  
**Epitope** SLLNATDIAV  
**Epitope name** Env813  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- None of the 17 HIV-infected HLA-A2+ people in this study recognized this epitope.

**HXB2 Location** gp160 (813–822)  
**Author Location** gp160 (813–822)  
**Epitope** SLLNATDIAV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding

**Keywords** acute/early infection, optimal epitope

**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was recognized both in acute and chronic infection, but slightly more frequently in chronic infection.

**HXB2 Location** gp160 (813–822)  
**Author Location** Env

**Epitope** SLLNATAIAV

**Epitope name** A2-SAV10(Env)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (813–822)  
**Author Location** gp41

**Epitope** SLLNATDIAV

**Epitope name** gp41 SV10

**Immunogen** HIV-1 infection

**Species (MHC)** human (A68)

**Keywords** binding affinity, subtype comparisons, super-type, computational epitope prediction

**References** Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-super motif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- This epitope binds to three HLA-A2 supertype alleles: A\*6802 (highest affinity), A\*0202 and A\*0203 (but not A\*0201 and not A\*0206)

- This epitope did not elicit an ELISPOT response in 22 chronic HIV HLA-A2 infections, but elicited a strong response in 1/12 acute HLA-A2 infections – this individual, AC13, was HLA A\*0201/68 B44/14 and also had a strong response to HLA-A2 vpr epitope AIIRILQQL.

**HXB2 Location** gp160 (813–828)

**Author Location** gp41 (MN)

**Epitope** SLLNATAIAVAEGTDR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** assay standardization/improvement, HAART, ART

**References** Chitnis *et al.* 2003

- 17 perinatally HIV-1 infected children (0.08–16 years) were evaluated for HLA-A2-restricted IFN-gamma CD8+ CTL responses against 4 immunodominant peptides that carry HLA-A2 epitopes. Two peptides were from gp120 (one at position 112, one from the V3 loop), and one each was from gp41 and Gag. 15/17 patients responded to the Gag peptide, 13/17 to the gp41 and the non-V3 gp120 peptides, and 11/17 responded to the V3 loop. 4 children recognized all 4 peptides.

**HXB2 Location** gp160 (814–822)

**Author Location** Env (815–823)

**Epitope** LLNATAIAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity

**References** Kmiecik *et al.* 1998a

- CTL responses in six patients to four Env epitopes were studied: D2: LLNATAIAV, 5.3: RLRDLLLIV, D1: KLTPLCVTL, and 4.3: QMHEDIISL—all have A2 anchor residues.
- The C terminal epitopes (D2 and 5.3) were highly variable and the variability was considered responsible for limited CTL response, while D1 and 4.3, N-terminal epitopes, were much more conserved and gave evidence of high levels of CTL response *in vitro*.
- Peptides 5.3 and D2 bound to HLA A\*0201 with low affinity and were variable, particularly D2.
- Substitutions in peptide D2: llnTiAiav did not abrogate the response, but diminished it.
- In a longitudinal study, the CTL response to the variable D2 epitope diminished over time, while the response to the conserved epitope D1 stayed higher.

**HXB2 Location** gp160 (814–822)

**Author Location** (C consensus)

**Epitope** LLDTIAIAV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** gp160 (814–822)

**Author Location** (C consensus)

**Epitope** LLDTIAIAV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- LLDTIAIAV is an optimal epitope.

**HXB2 Location** gp160 (814–822)

**Author Location** Env

**Epitope** LLNATAIAV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background

and HIV-1 epitope-immune response interaction account for nonprogression of disease.

- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This HLA-A\*02/A\*0201 restricted epitope, LLNATAIAV was mutated to LLNAiAIAV in the daughter D2 isolate.

**HXB2 Location** gp160 (814–822)

**Author Location** gp41 (815–823 LAI)

**Epitope** LLNATDIAV

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160

**Species (MHC)** human (A2)

**References** Dupuis *et al.* 1995

- Of two CTL clones, one reacted only with 815-823, the other with 814-823 and 815-823.

**HXB2 Location** gp160 (814–822)

**Author Location** Env (815–823)

**Epitope** LLNATAIAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Kmiecik *et al.* 1998b

- Increased CTL response to cells expressing a VV construct ΔV3 mutant compared with a full-length env gene product.

**HXB2 Location** gp160 (822–832)

**Author Location** gp41 (SF2)

**Epitope** VAEGTDRVIEI

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of individuals that had a CTL response to this epitope (HLA presenting molecule uncertain) broken down by group: 0 group 1, 1 group 2, and 0 group 3.

**HXB2 Location** gp160 (824–832)

**Author Location** gp160 (828–836 WEAU)

**Epitope** EGTDRIVIEI

**Epitope name** gp160 EI9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*2902, B\*0801, B\*4403

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** dynamics, immunodominance, acute/early infection, kinetics, characterizing CD8+ T cells, viral fitness and reversion

**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- This was one of five reasonably strong responses in early infection in the patient WEAU, and the epitope sequence did not vary during the first year of the infection.

**HXB2 Location** gp160 (827–841)

**Author Location** gp41 (834–848 IIIB)

**Epitope** DRVIEVVQGAYRAIR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Clerici *et al.* 1991a

- Helper and cytotoxic T cells can be stimulated by this peptide (Th4)

**HXB2 Location** gp160 (827–841)

**Author Location** gp41 (834–848 IIIB)

**Epitope** DRVIEVVQGAYRAIR

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>p</sup>, H-2<sup>q</sup>, H-2<sup>u</sup>)

**References** Shirai *et al.* 1992

- In a murine system multiple class I molecules can present to CTL.

**HXB2 Location** gp160 (827–841)

**Author Location** gp41 (834–848 IIIB)

**Epitope** DRVIEVVQGAYRAIR

**Immunogen** vaccine

*Vector/Type:* vaccinia *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>p</sup>, H-2<sup>q</sup>, H-2<sup>u</sup>)

**References** Shirai *et al.* 1996b

- Multiple murine MHC can cross-present this epitope (HP53), and P18 RIQRGPGRAFVTIGK, to specific CTL.

**HXB2 Location** gp160 (827–841)

**Author Location** gp41

**Epitope** DRVIEVVQGAYRAIR  
**Epitope name** N15  
**Subtype** A, B, C  
**Immunogen** vaccine  
*Vector/Type:* DNA, virus-like particle (VLP),  
 polypeptide *HIV component:* Env, Gag,  
 Nef, Pol  
**Species (MHC)** mouse (H-2a, H-2d)  
**Assay type** CD8 T-cell ELISpot - IFN $\gamma$ , Other  
**Keywords** assay standardization/improvement, vaccine-  
 specific epitope characteristics, vaccine anti-  
 gen design, antibody generation  
**References** Karpenko *et al.* 2007

- A combined VLP-based vaccine, CombiHIVvac, was designed comprising TBI with 4 T-cell epitopes and 5 B-cell epitopes, as well as TCI with over 80 T-cell epitopes from Env, Gag, Pol and Nef conserved across A, B and C HIV-1 subtypes. The vaccine induced humoral and cellular immunity in mice infected with 3 HIV-1 strains. Virus-neutralizing activity was as efficient as HIV-1 patient sera inhibition of viral replication. IFN-gamma and IL-2 ELISpot showed that CTL responses were induced, though at 2 & 10 times lower than T-helper responses as measured by IL-4 ELISpot. Toxicity studies showed the vaccine to be promising with no allergenic properties.
- This multiple class I restricted peptide, DRVIEVVQ-GAYRAIR, is from the TCI component of the vaccine. It induced CTL responses as measured by ELISpot.

**HXB2 Location** gp160 (827–841)  
**Author Location** gp41 (834–848 III B)  
**Epitope** DRVIEVVQGAYRAIR  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human  
**References** Pinto *et al.* 1995  
 • CTL and T helper cell reactivity in healthcare workers exposed to HIV.

**HXB2 Location** gp160 (828–836)  
**Author Location** Env (829–837 subtype B)  
**Epitope** RVIEVLQRA  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160  
**Species (MHC)** human (A\*0201)  
**Keywords** binding affinity  
**References** Kundu *et al.* 1998a

- Ten HIV-1 + HLA A2 asymptomatic individuals were given two courses of HIV-1 MN rgp160 vaccine over a 2 year period.
- Two hundred and fifty three HIV-1 peptides of 9 or 10 aa possessing the HLA-A2.1 binding motif (Leu at position 2, Val at the C terminus) were identified in gp160, of which 25 had a high or intermediate binding affinity.
- Eleven peptides were studied that had high HLA-A2 binding affinity – a CTL response was detected to 9/11 peptides in at least 1 individual.
- CTL responses after reimmunization may include recall responses – individuals with vaccine cross-reactive sequences prior to vaccination showed detectable CTL responses.

**HXB2 Location** gp160 (828–836)  
**Author Location** gp41 (829–837 LAI)  
**Epitope** RVIEVLQRA  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160  
**Species (MHC)** human (A2)  
**References** Dupuis *et al.* 1995  
 • CTL from HLA-A2 positive subject react with this peptide.

**HXB2 Location** gp160 (828–836)  
**Author Location** gp41 (829–837 CM243 subtype CRF01)  
**Epitope** KVIEVAQGA  
**Subtype** CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** subtype comparisons  
**References** Bond *et al.* 2001  
 • More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.  
 • 1/4 tested FSWs recognized the E clade version of this epitope, which differs from the previously defined B clade version by three amino acids, RvievLqRa.  
 • This epitope was only conserved in CRF01 (subtype E), and identities were rare.

**HXB2 Location** gp160 (830–854)  
**Author Location** gp41 (831–853)  
**Epitope** IEVVQAYRAIIRHPRIRQGLERI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Price *et al.* 1995  
 • Study of cytokines released by HIV-1 specific activated CTL.

**HXB2 Location** gp160 (831–838)  
**Author Location** Env (830–837)  
**Epitope** EVAQRAYR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3303)  
**References** Hossain *et al.* 2001; Takiguchi *et al.* 2000  
 • HLA-A33 a very common allele in Asia, with HLA-A\*3303 the most common among the Japanese. New A\*3303 epitopes were defined to better characterize the immune response in this population.  
 • The anchor motif for HLA\*3303 (A, I, L, V, F, Y in position 2 (F and Y bind most strongly), and R (K is also tolerated) in the C-terminal position) was used to define 82 potentially reactive peptides in Env; 37/82 peptides bound to A\*3303; 3/37 peptides could induce peptide-specific CTL in bulk PBMC cultures from 1/3 HLA A\*3303 positive individuals tested.  
 • 2/3 peptides that reacted with the bulk culture, EVAQRAYR and VIEVAQRAYR, were overlapping, with one encompassing the other, but EVAQRAYR was shown to be the one that was reactive with a CTL clone.



- CTL clones were isolated that killed target cells in a concentration dependent manner after pulsing with the EVAQRAYR peptide, that could also kill cells transfected with env expressed from a vaccinia vector. Bulk cultures were tested from six additional people, and only 2/6 reacted with this peptide, but the peptide is in a highly variable region.

**HXB2 Location** gp160 (831–838)  
**Author Location** gp41 (320–327)  
**Epitope** EVAQRAYR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*3303)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** gp160 (833–841)  
**Author Location** gp160 (837–845 WEAU)  
**Epitope** VQRTCRAIL  
**Epitope name** gp160 VL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*2902, B\*0801, B\*4403  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** dynamics, immunodominance, acute/early infection, characterizing CD8+ T cells, viral fitness and reversion  
**References** Jones *et al.* 2004

- Primary CD8+ T-cell response to Env, Tat and Gag and the extent, kinetics and mechanisms of viral escape were examined in three patients. Rapid escape, within weeks from infection, from HIV specific CTL responses was observed in all three patients, but the kinetics and extent of the escape differed depending on the breadth and co-dominant distribution of CTL-mediated pressure. The two patients that rapidly declined had more focused immunodominant responses, while the single patient that had low viral load and stable CD4 counts for seven years had a broad co-dominant response and less escape.
- The patient WEAU had high viral loads and rapid CD4 decline. WEAU mounted 14 detected CTL responses, with distinct patterns of immunodominance. WEAU did not control viral replication well, and escape mutations occurred early and 4/14 had changes that could have resulted in escape, and two were confirmed as escape.
- This was one of five reasonably strong responses in early infection in the patient WEAU, and the epitope sequence did not vary during the first year of the infection.

**HXB2 Location** gp160 (833–847)  
**Author Location**  
**Epitope** LQRAGRAILHIPTRI  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox prime with gp120 boost *Strain:* Other *HIV component:* gp160  
**Species (MHC)** human  
**Donor MHC** A3, A33; B15 (63), B27

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** gp160 (835–843)  
**Author Location** Env (834–842 SF2)  
**Epitope** RAYRAILHI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5101)  
**Keywords** rate of progression  
**References** Tomiyama *et al.* 1999

- HLA-B27, -B51, and -B57 are associated with slow progression to AIDS, while HLA-B35, -B8, -B24 are associated with a rapid progression to AIDS (Nat. Med. 2:405, 1996; Lancet 22:1187, 1986; Hum Immunol 22:73, 1988; Hum Immunol 44:156, 1995)
- 15% of Japanese populations carry HLA-B51 while HLA-B27 and -B57 are detected in less than 0.3%
- Of the 172 HIV-1 peptides with HLA-B\*5101 anchor residues, 33 bound to HLA-B\*5101, seven of these peptides were reactive with CTL from 3 B\*5101 positive individuals, and six were properly processed.
- This peptide could stimulate CTL from one person, however this CTL clone did not recognize B\*5101 positive target cells infected with HIV-1 recombinant vaccinia expressing Env, so it was not confirmed that this peptide was a properly processed epitope.

**HXB2 Location** gp160 (835–843)  
**Author Location** Env (835–843)  
**Epitope** RAYRAILHI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B51)  
**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8  
**Country** Netherlands  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, escape  
**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.

- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. The rTFrailhi variant residues arose at early time points, rlyrailhX variant residues arose at intermediate time points.

**HXB2 Location** gp160 (837–856)  
**Author Location** gp120 (844–863 LAI)  
**Epitope** YRAIRHIPRRIRQGLERILL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**References** Shankar *et al.* 1996

**HXB2 Location** gp160 (837–856)  
**Author Location** gp41 (844–863 HXB2)  
**Epitope** YRAIRHIPRRIRQGLERILL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**References** Lieberman *et al.* 1992

- CTL epitope defined by T cell line and peptide mapping.

**HXB2 Location** gp160 (837–856)  
**Author Location** gp120 (844–863)  
**Epitope** YRAIRHIPRRIRQGLERILL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** gp160 (837–856)  
**Author Location** gp120 (844–863 SF2)  
**Epitope** YRAIRHIPRRIRQGLERILL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI gp160.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2, A26, B7, and B38.

**HXB2 Location** gp160 (841–855)  
**Author Location** Env (837–851)  
**Epitope** LHIPTRIRQGLERAL  
**Epitope name** EE211  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** rate of progression, acute/early infection, memory cells  
**References** Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to peptide EE211, LHIPTRIRQGLERAL, a patient with early ART had IFN-gamma secretion by both CD127 hi and lo cells before treatment but was maintained in CD127 hi cells after treatment. CD127 hi cells were responsible for producing IL-2 and TNF-alpha after ART.

**HXB2 Location** gp160 (842–856)  
**Author Location** gp41 (SF2)  
**Epitope** HIPRRIRQGLERALL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Altfield *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- The only Env peptide recognized was gp41 HIPRRIRQGLERALL.

**HXB2 Location** gp160 (842–856)  
**Author Location** gp41  
**Epitope** HIPRRIRQGLERALL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J. Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, HIPRRIRQGLERALL, had an overall frequency of recognition of 16.7% - 15.3% AA, 23.1% C, 15.9% H, 14.3% WI.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41 (843–851)

**Epitope** IPRRRIRQGF

**Epitope name** IF9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07)

**Country** Kenya

**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement

**References** McKinnon *et al.* 2007

- The authors suggest that epitope variation has different effects on the HIV- specific immune responses of effector memory T cells (Tem) and central memory T cells (Tcm). They show a lack of correlation between IFN-gamma ELISPOT (Tem typical) and proliferation (Tcm typical) assays for specific epitopes in subjects. Since proliferating CTL also correlate with high intracellular IFN-gamma levels, they surmise that proliferating Tcm differentiate to express Tem functions.
- They also show that proliferating CTL numbers correlate with higher CD4 cell counts.
- Several patients responded strongly to epitope variants that were not part of their autologous HIV-1 sequences. Thus they suggest more comprehensive functional characterizations than the usual overnight IFN-gamma ELISPOTS as well as assessments of Tem versus Tcm specific responses rather than general CTL immune responses.
- 4 variants of this index epitope IPRRRIRQGF, IF9, were tested - IPtRIRQGI, IPRRRIRQGa, IPtRIRQGF, IPvRIRQGI. Variant IPRRRIRQGa that is relatively rare induced a high proliferation rate in T cells.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41 (332–340)

**Epitope** IPRRRIRQGL

**Epitope name** IL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07)

**Assay type** CTL suppression of replication

**Keywords** class I down-regulation by Nef

**References** Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Late protein Env epitope IPRRRIRQGL-recognizing CTLs were affected by Nef.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41 (848–856 LAI)

**Epitope** IPRRRIRQGL

**Subtype** B

**Immunogen**

**Species (MHC)** human (B\*0702)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0702 epitope.

**HXB2 Location** gp160 (843–851)

**Author Location**

**Epitope** IPRRRIRQGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B07)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope IPRRRIRQGL elicited a magnitude of response of 163 SFC with a functional avidity of 1nM and binding affinity of 8.3nM.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41 (848–856 LAI)

**Epitope** IPRRRIRQGL

**Subtype** B

**Immunogen**

**Species (MHC)** human (B7)

**Keywords** mother-to-infant transmission

**References** Brander & Walker 1995

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

**HXB2 Location** gp160 (843–851)

**Author Location**

**Epitope** IPRRRIRQGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** immunodominance, escape

**References** Soudeyns *et al.* 1999

- Following primary infection, progressive diversification and accumulation of mutations of HIV-env nucleotide sequences was observed, focused in V2 in one individual and in V8 in another.
- The patient with the V2 diversification showed only transient CTL against Env and Nef.

- The patient with the V8 diversification had an immunodominant CTL response to V8 epitope IPRRIRQGL, and multiple escape variants emerged within a year: ipTrirqgl and ipTrirqgF, which abrogated the CTL response *in vitro*, and also iprrLqgl and iprrirQDl which gave diminished responses.

**HXB2 Location** gp160 (843–851)  
**Author Location** gp41 (848–856 LAI)  
**Epitope** IPRRIRQGL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** subtype comparisons  
**References** Cao *et al.* 1997a

- The consensus peptide of clades A, B, D, and F is IPRRIRQGL.
- The consensus peptide of clade C is iprrirqgF, and it is equally reactive.

**HXB2 Location** gp160 (843–851)  
**Author Location** gp41 (848–856 subtype B)  
**Epitope** IPRRIRQGL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** subtype comparisons, acute/early infection  
**References** Wilson *et al.* 1998b

- The extent of CTL interclade cross-reactivity from CTL isolated from individuals newly infected with B clade virus was studied, and extensive cross-reactivity was observed.
- Two HLA B7 individuals had CTL response to B\_LAI, A\_92UG037 and C\_92BR025 gp160, but were B clade strain MN non-responders – the authors note that the B7 epitope IPRRIRQGL is conserved between the LAI and clade A and C strains, but that MN has a non-conservative Arg to Thr substitution at position three that may be contributing to the specificity of the response in the HLA B7 individuals.

**HXB2 Location** gp160 (843–851)  
**Author Location** gp41 (843–851 HXB2)  
**Epitope** IPRRIRQGL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** rate of progression, immunodominance  
**References** Hay *et al.* 1999

- CTL response to IPRRIRQGL was the immunodominant response in a rapid progressor – there was a subdominant response to SPAIFQSSM in Pol, and interestingly, no response to commonly immunodominant HLA A\*0201 epitope SLYNTVATL, although this individual was HLA A\*0201.
- The individual showed a strong initial CTL response at the time of the initial drop in viremia, but it was quickly lost, although memory cells persisted.
- Despite the initial narrow response to two epitopes, no other CTL responses developed.
- No HIV-specific lymphoproliferative responses were detected in this patient, and neutralizing antibody response was weak.

- Variants were observed *in vivo*, the most common form of the viral epitope at presentation at 3 months was the only form that did not elicit a CTL response: iprTrqgl; the other forms detected were iprrirqgF, iprrLqgF, VprirqgF and they could elicit a CTL response although the response to iprrLqgF was reduced.
- A second rapid progressor had a detectable CTL response exclusively to this epitope.

**HXB2 Location** gp160 (843–851)  
**Author Location** gp41 (subtype A)  
**Epitope** IPRRIRQGF  
**Subtype** A  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** subtype comparisons  
**References** Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.
- This optimal epitope sequence, recognized by CTL derived from a Ugandan with an A subtype infection, is cross-reactive with subtypes A and B, but not in subtype D.

**HXB2 Location** gp160 (843–851)  
**Author Location** gp41  
**Epitope** IPRRIRQGL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** rate of progression, acute/early infection  
**References** Islam *et al.* 2001

- Subject 053i was followed longitudinally from acute infection through death, and had rapid progression to AIDS.
- This individual had a dominant response to IPRRIRQGL with strong *in vivo* activated responses and *in vitro* stimulated memory responses and a subdominant response to SPAIFQSSM – during the course of disease progression (4 Years), the functional CTL responses were lost and no sequence variation occurred with in both epitopes.
- At 3 months post-presentation, seven IPRRIRQGL CTL clones were obtained, five used the T-cell receptor V $\beta$  6S1 and J $\beta$  2.7 and had the CDR3 WAASS, two used V $\beta$ 16S1, ER-SPPGD, J $\beta$  2.7 and one CTL clone isolated at 39 months was V $\beta$  14S1, CR3 PTAAG, and J $\beta$  2.1 – all of these clones persisted over the course of the infection, even to time of death, despite the loss of CTL functional responses over time.

**HXB2 Location** gp160 (843–851)  
**Author Location** gp41 (843–851 SF2)  
**Epitope** IPRRIRQGL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 2/4 group 1, 1/3 group 2, and 1/1 group 3.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41 (848–856)

**Epitope** IPRRIRQGL

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B7)

**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- IPRRIRQGL cross-reacts with clades A, B and D.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B7 women, 2/5 HEPS and 5/6 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 2 of the 5/6 HIV-1 infected women that responded to the epitope, but in neither of the 2/5 HEPS cases.
- Subject ML 1203 started with CTL responses to A\*6802 DTVLEDINL and to B7 FVPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A\*6802 ETAYFILKL which became dominant, B7 TPGPGV/IRYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41 (843–851)

**Epitope** IPRRIRQGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2–8 out of 11 B7-restricted epitopes.
- An acute seroconverter homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41 (SF2)

**Epitope** IPRRIRQGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41 (842–852)

**Epitope** IPRRIRQGL

**Epitope name** B7-IL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), immunodominance, acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- Only two epitopes were detected during acute infection in patient AC-06, B7 restricted gp41 epitope IPRRIRQGL and Gag GPGHKARVL. GPGHKARVL was the first targeted peptide, and remained immunodominant through the 34 month study period.
- 6/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** gp160 (843–851)**Author Location** gp41**Epitope** IPRRRIRQGL**Epitope name** B7-IL9(gp41)**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Donor MHC** A24, B27, B7**Keywords** HAART, ART, supervised treatment interruptions (STI)**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient C displayed the greatest response to B27-KK10(p24), and in decreasing order also responded to A24-RW8(Nef), B7-IL9(gp41), A24-RL9(gp41), A24-YL8(gp41), and B7-TM9(Nef).

**HXB2 Location** gp160 (843–851)**Author Location** Env**Epitope** IPRRRIRQGL**Epitope name** EW10**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** class I down-regulation by Nef**References** Bobbitt *et al.* 2003

- Nef, through Nef-mediated MHC-1 down-regulation, is not the only viral protein to influence levels of HIV-specific CTL recognition. The Rev L60F mutation, a common natural variant, can decrease CTL recognition of late gene products. The Rev mutation impacts the early to late gene switch, reducing late gene product production (Gag, Pol, Env, Vpu, Vpr and Vif), while increasing Nef production, both of which reduce the impact CTL recognition of late gene products. As expected, Rev L60F rendered HIV infected cells more resistant to CTL that recognized epitopes from the late proteins Env and Gag. Gag expression is reduced more than Env, and Gag-specific CTL were more profoundly affected. Conversely CTL

against an epitope in an early gene product, Tat, were more efficiently recognized when infected with viruses carrying the Rev L60F mutation.

- Patients in the asymptomatic phase with active immune responses had more CTL resistant viruses, with lower Rev activity, lower Gag expression and greater resistance to Gag-specific CTL killing, while viruses isolated from people with AIDS were more sensitive to CTL killing.

**HXB2 Location** gp160 (843–851)**Author Location** gp41 (843–851)**Epitope** IPRRRIRQGL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Donor MHC** A1, A3, B14, B7, Cw\*0702, Cw\*0802**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** binding affinity, acute/early infection, early-expressed proteins**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** gp160 (843–851)**Author Location** gp41**Epitope** IPRRRIRQGL**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Country** Netherlands**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** HIV exposed persistently seronegative (HEPS)**References** Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies

of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.

- 3/9 HLA B7+ infection-resistant men, compared to 0/4 pre-seroconversion men who went on to become infected, reacted to this epitope.

**HXB2 Location** gp160 (843–851)

**Author Location** Env (333–341)

**Epitope** IPRRRIRQGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/7 patients recognized this epitope.

**HXB2 Location** gp160 (843–851)

**Author Location** (B consensus)

**Epitope** IPRRRIRQGL

**Epitope name** IL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A31, A68, B07, B70, Cw1, Cw7

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41

**Epitope** IPRRRIRQGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** United Kingdom

**Assay type** Tetramer binding, T-cell Elispot, Intracellular cytokine staining

**Keywords** rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction

**References** Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41 (333–334)

**Epitope** IPRRRIRQGL

**Epitope name** IPR

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0–80% as efficiently as the index peptide, and the relatively efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- This was one of 8 reactive epitopes found not to vary over time.

**HXB2 Location** gp160 (843–851)

**Author Location** gp120

**Epitope** IPRRRIRQGL

**Epitope name** IL9

**Immunogen**

**Species (MHC)** (B7)

**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion

**References** Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** gp160 (843–851)

**Author Location** gp41

**Epitope** IPRRRIRQGL

**Epitope name** B7-IL9(gp41)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (843–851)

**Author Location** gp160 (clade A, B, C, D)

**Epitope** IPRRIRQGL

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*6802A\*6802, B\*1303, B\*1401, Cw\*0602, Cw\*1701

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

**References** McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. IPRRIRQGL responses were detected in all 4 clades in 1 woman: clade A gave a high response; IPRRIRQGL was identical clade B; clade C and D had lower responses and carried variant peptides IPRRIRQGL and IvRRIRQGL.

**HXB2 Location** gp160 (843–851)

**Author Location** gp160

**Epitope** IPRRIRQGL

**Subtype** A, B, C, D

**Immunogen** HIV-1 infection, vaccine

**Vector/Type:** vaccinia **Strain:** A clade, B clade, D clade NDK, C clade consensus  
**HIV component:** Env

**Species (MHC)** human

**Donor MHC** A\*0205, A\*3402, B\*4201, B\*5802, Cw\*0602, Cw\*1701

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

**References** McKinnon *et al.* 2005

- Interclade cross-reactivity of clades A, B, C, and D was tested using recombinant vaccinia-based IFN-gamma Elispot assay. 47/74 women had a positive Elispot response to at least one clade, and cross-clade responses were frequent. Clade A responses were most frequent, as expected, as clade A dominates the Kenyan epidemic (85% of the 47 women responded to clade A Env, 74% to B, 62% to C, and 43% to D). Cross-clade CD8 T-cell responses were common and directed at conserved epitopes.
- There was a greater magnitude of response to A clade peptides in individuals who responded to more than 1 clade; a 2-fold higher response was observed in clade A in 36% (9/25) of these individuals, and the response to A peptides was never lower. An IPRRIRQGL response was detected in a woman who had Env responses to 3 clades, A, B, and C, and clade A and B gave the highest responses. IPRRIRQGL was identical in A and B, had the form IPRRIRQGL in C, and IvRRIRQGL in D.

**HXB2 Location** gp160 (843–851)

**Author Location**

**Epitope** IPRRIRQGL

**Immunogen** HIV-1 infection, vaccine

**Vector/Type:** canarypox prime with gp120 boost **Strain:** B clade LAI, B clade MN  
**HIV component:** Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A\*2501, A\*3002; B\*0702, B\*1801

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** gp160 (845–856)

**Author Location** gp41 (852–863 HXB2)

**Epitope** RRIRQGLERILL



**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (A30, B8)**References** Lieberman *et al.* 1992

- CTL epitope defined by T cell line and peptide mapping.

**HXB2 Location** gp160 (845–856)**Author Location** gp41 (852–863 LAI)**Epitope** RRIRQGLERILL**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (B7)**References** Shankar *et al.* 1996**HXB2 Location** gp160 (846–854)**Author Location****Epitope** RIRQGLERA**Epitope name** Env-RA9**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (A\*0205)**Donor MHC** A\*0205, A\*3002, B\*1402, B\*5301, Cw\*0401, Cw\*0802**Keywords** HAART, ART**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Patient 00RCH28 was African American, not on HAART, had a viral load of 5900 and CD4 count of 889, and she also recognized IN(219-227), KIQNFRVYY, A\*3002.
- Among HIV+ individuals who carried HLA A02, 6/21 (29%) recognized this epitope.

**HXB2 Location** gp160 (846–854)**Author Location** gp41 (335–343)**Epitope** RIRQGLERA**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0205)**Keywords** optimal epitope**References** Frahm *et al.* 2008**HXB2 Location** gp160 (846–854)**Author Location** gp41 (846–859)**Epitope** RIRQGLERA**Immunogen****Species (MHC)** (A\*0205)**Keywords** subtype comparisons, viral fitness and reversion**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 30/50 Brazilian HIV sequences.

**HXB2 Location** gp160 (846–854)**Author Location** gp41**Epitope** RIRQGLERA**Epitope name** A0205-RA9(gp41)**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** gp160 (848–856)**Author Location** gp160 (848–856)**Epitope** RQGLERALL**Immunogen****Species (MHC)** human (B8)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes that this is an B8 epitope.

**HXB2 Location** gp160 (848–856)**Author Location****Epitope** RQGLERALL**Immunogen****Species (MHC)** (B8)**Keywords** review, immunodominance, escape, vaccine antigen design**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

**HXB2 Location** gp160 (848–856)**Author Location****Epitope** RQGLERALL**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A\*0101; B\*0801, B\*1401**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** vaccine-induced epitopes**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- RQGLERALL was recognized by a placebo patient after infection.

**HXB2 Location** gp160 (848–856)

**Author Location**

**Epitope** RQGLERALL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A1, A2; B38, B8

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** gp160 (849–856)

**Author Location** gp41 (849–856)

**Epitope** QGLERALL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A1A1, B14, B8, Cw7, Cw8

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance

of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.

- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

## II-B-22 Env CTL/CD8+ epitopes

**HXB2 Location** Env

**Author Location**

**Epitope**

**Immunogen** computer prediction

**Species (MHC)** (A\*0201, B\*3501)

**Keywords** subtype comparisons, computational epitope prediction

**References** Schönbach *et al.* 2002

- Computational methods (artificial neural networks, hidden Markov models, binding matrices based on HLA association rates) were used to identify HLA-A\*0201 and HLA-B\*3501 HIV T-cell epitope candidates from 533 Gag, Env and Pol sequences of which 374 were derived from HIV-1, 97 were derived from HIV-2 and 62 from SIV. Comparisons to known epitopes and between clades were made.

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** A, B, C

**Immunogen** vaccine

*Vector/Type:* canarypox prime with gp120 boost, canarypox prime with gp160 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Nef, Pol

**Species (MHC)** human (A1, A2, A24, A25, A26, A30, A31, B17, B39, B51, B57, B60, B62, B70, B8)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Ferrari *et al.* 2001

- Different HIV strains were used for different regions: gp41 LAI, Gag LAI, gp120 MN, gp120 SF2
- HLA-B62 responses dominated the responses against an Env vaccine in an individual (022JAV) who was HLA A2, A26, B35, B62. The strongest response was against the MN peptide 381-400; a response diminished by half was observed against vaccinia expressed clade A and clade C relative to clade B.
- Class I presentation of Env CTL responses in vaccinee 022A12K: A25 > B39, A1 and B8 were undetectable.

- Class I presentation of Env CTL responses in vaccinee 022A12N: B57 » A2 > A26 and B60.
- Class I presentation of Env CTL responses in vaccinee 034GP3: A31 > A24 > B62 > B51.
- Class I presentation of Env CTL responses in vaccinee 0348PP: B17 > B70, A1 and A30 were undetectable.

**HXB2 Location** Env**Author Location** gp120 (303–327)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human (A11, A2, A3, B27)**Keywords** subtype comparisons**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.
- For this cluster of epitopes spanning the tip of the V3 loop, they suggest including a sequence from each clade.

**HXB2 Location** Env**Author Location****Epitope****Subtype** B**Immunogen** vaccine

*Vector/Type:* canarypox prime with gp120 boost, canarypox prime with gp160 boost  
*Strain:* B clade LAI, B clade MN, B clade SF2  
*HIV component:* Gag, gp120, gp41, Nef, Pol

**Species (MHC)** human (A2, B8)**Keywords** vaccine-induced epitopes**References** Ferrari *et al.* 2001

- Different HIV strains were used for different regions: gp41 LAI, Gag LAI, gp120 MN, gp120 SF2
- No HLA-A\*0201 or B8 responses were made against the Env vaccine in individuals carrying these alleles, despite these being common presenting molecules for CTL responses to natural infections.

**HXB2 Location** Env**Author Location** Env**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*35)**Keywords** rate of progression**References** Jin *et al.* 2002

- Patients with HLA-B\*35 variants B\*3502, B\*3503, B\*3504, and B\*5301 tend to proceed to AIDS more quickly than those with B\*3501.
- Of 32 patients with HLA-B\*35 alleles CD8+ CTL responses were quantified using an intracellular cytokine staining assay – 75% had responses to Pol, 69% to Gag, 50% to Nef, and 41% to Env.
- The overall magnitude of CTL responses did not differ between those bearing B\*3501 and the others. A higher percentage of Gag responses was observed in those that had lower

RNA levels that carried B\*3501, and there was a negative association with viral load and CTL activity. The data is consistent with higher levels of CTL responses contributing to protection in B\*3501 individuals, but not in B\*3502, B\*3503, B\*3504, and B\*5301 individuals.

**HXB2 Location** Env**Author Location** gp41 (842–850 IIIB, BH8)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human (B7)**References** Pantaleo *et al.* 1997; Soudeyns & Pantaleo 1997

- Clonotype-specific PCR and analysis of *in vivo* HIV-specific CTL showed that in early infection HIV-specific CTL clones preferentially accumulate in blood rather than lymph nodes and that they accumulate prior to down-regulation of virus.

**HXB2 Location** Env**Author Location** gp120 (318–327 IIIB)**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade IIIB*HIV component:* gp120**Species (MHC)** mouse (H-2 Dd)**Assay type** Cytokine production, Intracellular cytokine staining, Th support of CTL response, Chromium-release assay**Keywords** epitope processing, Th1, vaccine antigen design**References** Vatakis *et al.* 2005

- Mice were vaccinated with three DNA epitope vaccines, differing in the affinity of the helper epitope to the MHC class II molecule. It was observed that a TH epitope with lower affinity decreased the magnitude of the CTL responses and decreased the numbers of epitope-specific T-helper cells and CTLs. Also, cytokine secretion and proliferative responses were diminished.

**HXB2 Location** Env**Author Location** gp160 (MN)**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade MN*HIV component:* gp120, gp160**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Vinner *et al.* 1999

- Mammalian codon optimization renders gp160 expression Rev independent, increases gp160 expression levels, and DNA vaccination of BALB/c mice yields a higher antibody response with an earlier onset than wild type.
- Secreted gp120 gave higher antibody titers than membrane bound gp160.
- In contrast to antibodies, synthetic codon-optimized DNA did not alter the CTL response, wild type genes generated equally strong CTL responses.

**HXB2 Location** Env**Author Location** (IIIB)**Epitope**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* V3  
*Adjuvant:* Cholera toxin (CT), GM-CSF, IL-4

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Kato *et al.* 2000

- A multicomponent peptide vaccine VC1 with cholera toxin adjuvant was given to mice.
- Immunization of BALB/c mice with VC1 and CT induced a strong CTL response which was enhanced by IL-12 expressing plasmids.
- Immunization with VC1 and CT resulted in HIV-1 specific IgA antibody responses, which were increased by the combination of IL-4 or GM-CSF expressing plasmids.

**HXB2 Location** Env

**Author Location** gp160 (IIIB)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* PLG

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Kaneko *et al.* 2000

- A PLG-microparticle encapsulated DNA encoding gp160 was given to mice.
- Oral DNA vaccination of BALB/c mice induced mucosal and systemic gp160 glycoprotein-specific cellular and humoral immune responses, and mice vaccinated orally had higher resistance to HIV-env expressing vaccinia intrarectal challenge than mice vaccinated i.m.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor with cationic liposome *HIV component:* gp160, Rev

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Ishii *et al.* 1997

- pCMV160/Rev is a DNA vaccine candidate carrying gp160 and Rev linked to a cytomegalovirus (CMV promotor)

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** vaccine

*Vector/Type:* adeno-associated virus (AAV)  
*HIV component:* Env, Rev, Tat *Adjuvant:* IL-2

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Xin *et al.* 2001

- An AAV vector expressing HIV-1 env, tat, and rev genes (AAV-HIV vector) was used to vaccinate BALB/c mice.
- A single injection stimulated and long lasting serum IgG, fecal IgA, and HIV-specific CTL.
- Boosting enhanced the humoral response, and IL2 enhanced T-cell immunity.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** vaccine

*Vector/Type:* vaccinia, influenza *Strain:* B clade IIIB *HIV component:* Env, V3

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Gonzalo *et al.* 1999

- The use of two different live vectors for priming and boosting has a synergistic effect on the immune response against HIV-1— a 5-6 fold enhanced CTL response in Balb/c mice occurred when they were immunized with rec influenza virus (Flu-Env) expressing the V3 loop epitope from HIV-1 strain IIIB, and boosted with a vaccinia virus recombinant (VV-Env) expressing the complete HIV-1-IIIB env protein, compared to either immunogen alone.

**HXB2 Location** Env

**Author Location** Env (subtype B)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* rabies virus *Strain:* B clade 89.6, B clade NL43 *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** McGettigan *et al.* 2001

- BALB/c were immunized with a replication competent recombinant rabies virus (RV) vaccine expressing HIV-1 gp160.
- A single vaccination induced induced strong and long-lasting (4.5 months) gp160-specific CTL cytotoxic responses.
- Although the greatest specific lysis was achieved when the vaccine strain was also used as the *in vitro* the target strain to assess the response, there was extensive CTL cross-reactivity against other B clade HIV-1 envelope proteins, implying CTL recognition of multiple epitopes within the HIV-1 envelope protein.

**HXB2 Location** Env

**Author Location** gp120 (V3)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, polyepitope *Strain:* B clade BRVA, B clade IIIB, B clade JY1, B clade LR150, B clade MN, B clade RF *HIV component:* V3

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Vázquez-Blomquist *et al.* 2003

- Priming mice with recombinant MVA and boosting with fowlpox was shown to increase the number of specific IFN-gamma secreting cells relative to reversing the order (fowlpox prime, MVA boost) or priming with a Semliki Forest Virus DNA vector and boosting with recombinant MVA or fowlpox. The authors speculate why the order might be important. Fowlpox has more proteins, so there may be more CTL epitope competition; alternatively pox viruses may modulate the immune response through chemokine homologs.

- The antigen tested was a V3 loop polyepitope vaccine combining multiple V3 loop variants given by an intraperitoneal route to BALB/c mice.

**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* gp120  
*Adjuvant:* Cholera toxin (CT)  
**Species (MHC)** mouse (H-2D<sup>d</sup>)  
**Assay type** T-cell Elispot, Chromium-release assay  
**References** Bagley *et al.* 2003

- BALBc mice were immunized intramuscularly with single plasmids encoding gp120, or cholera toxin catalytic domain (CTA1) and gp120, or with a dicistronic DNA vaccine expressing both CTA1 and gp120. Vaccination including CTA elicited stronger and longer lasting Ab responses and T-cell responses to gp120.

**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Epitope name** p11c, p68A, p41A, p199A  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade 89.6P *HIV component:* Env  
**Species (MHC)** macaque (Mamu-A\*01)  
**Assay type** Tetramer binding, Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-specific epitope characteristics, immunodominance, vaccine antigen design  
**References** Subbramanian *et al.* 2006

- Multiepitope plasmid DNA vaccine constructs were shown to elicit CTL populations that do not show skewing of recognition of dominant epitopes in macaques, but repeated boosting of the vaccinated macaques uncovered and amplified the usual CTL epitope dominance hierarchy. This study suggests that heterologous prime-boost regimens can be effective in augmenting the magnitude of CTL responses, but cannot alter the dominance hierarchy established immediately after the exposure to antigen.
- Also, for live recombinant boost studies, results of in vitro peptide stimulation of PMBCs predict reliably the actual breadth of CTL responses that would expand out in antigen-primed T-cell populations.

**HXB2 Location** Env  
**Author Location** Env (SIV)  
**Epitope**  
**Immunogen** SIV infection  
**Species (MHC)** macaque (Mamu-A\*11, Mamu-B\*03, Mamu-B\*04, Mamu-B\*17)  
**References** Dzuris *et al.* 2000

- Cell binding assays for Mamu molecules were employed to describe the peptide binding motifs for Mamu-A\*11, -B\*03, -B\*03, -B\*04, and -B\*17 CTL epitopes – a similarity for Mamu-A\*11 and -B\*03 and human HLA-B\*44 and -B\*27,

respectively, was observed – all epitopes studied were SIV epitopes, so not specifically listed here.

**HXB2 Location** Env  
**Author Location** gp160 (LAI, MN)  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Protease

**Species (MHC)** human  
**References** Belshe *et al.* 1998

- The live canarypox vaccine ALVAC-HIV(vCP205) carrying MN gp120, LAI gp41, Gag and Protease, and boosted with SF-2 rpg120, was given to HIV-1 seronegative volunteers – HIV-specific Env or Gag CD8+ CTL were detected in 64% of the volunteers.

**HXB2 Location** Env  
**Author Location** gp160 (LAV)  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** epitope processing, dendritic cells  
**References** Zheng *et al.* 1999

- Protein delivery (gp160 LAV, p66 LAV, and p24 NY5) to human dendritic cells (DC) with liposomes provides enhanced memory CTL response relative to delivery of protein alone.
- Chloroquine administration enhanced epitope presentation, and brefeldin A and peptide aldehyde inhibitors inhibited antigen presentation, suggesting epitopes were processed by classical proteasome pathway.

**HXB2 Location** Env  
**Author Location** Env (IIIB)  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** rate of progression, Th1  
**References** Wasik *et al.* 2000

- HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of IL-2, as well as beta-chemokines, relative to other HIV+ infants.
- No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors.
- CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccinia/HIV constructs.

**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HAART, ART  
**References** Soudeyns *et al.* 2000

- Analysis of T cell receptor beta chain variable region repertoire indicates that antiretroviral therapy (ART) and highly active antiretroviral therapy (HAART) decrease global CD8 T cell oligoclonality during primary HIV infection.
- A sharp decline in HIV-1 gp120-specific CTL clones was observed in HAART-treated subjects.

**HXB2 Location** Env**Author Location** Env (LAI, MN)**Epitope****Immunogen** vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp41, Protease, V3

**Species (MHC)** human**References** Salmon-Ceron *et al.* 1999

- The vaccine used was a rec canarypox with HIV-1 gp120 MN, tm/gag/protease LAI (vCP205), alone or with p24E-V3 MN synthetic peptide (CLTB-36)
- Twenty HIV negative subjects were vaccinated in phase I trial with combinations of vCP205 and CLTB-36.
- Immunization with vCP205 induced HIV-1-specific ABs to gp120, V3, and p24 antigens, and CTL immune responses against vCP205 were detected after the fourth immunization in 33% of the subjects against Env, Gag and Pol, but the CLTB-36 peptide did not produce AB or CTL immune responses against p24 or gp160.

**HXB2 Location** Env**Author Location** Env**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** TCR usage**References** Gamberg *et al.* 1999

- 13/13 subjects with advanced HIV infections showed CD8 T cell proliferation and differentiation of CTL *in vitro*, and six individuals showed HIV-specific responses to Gag, Pol, Env or Nef antigens.
- Data suggests that the functional and genetic integrity of the CD8 T cell repertoire (TCR beta V gene intrafamily genetic diversity) remains intact through advanced HIV infection, although HIV-specific CTL activity decreases.

**HXB2 Location** Env**Author Location** Env (LAI, MN)**Epitope****Immunogen** vaccine

*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade SF2 *HIV component:* Env, Gag, Nef, Protease

**Species (MHC)** human**References** Gorse *et al.* 1999b

- The vaccine used was rec canarypox expressing HIV-1 env, gag, pol, nef and protease (vCP300) with or without administration of HIV-1 SF-2 rgp120.
- *In vitro* inducible CTL activity against HIV-1 Env, Gag, Pol, and Nef antigens was observed in 79% (15 of 19) of vaccine recipients.

- The combination of vCP300 and vP1291 together resulted in an overall increase in CTL induction and detection sensitivity.

**HXB2 Location** Env**Author Location** Env (LAI)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Buseyne *et al.* 1998b

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes.

**HXB2 Location** Env**Author Location** gp120 (IIIB)**Epitope****Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade IIIB *HIV component:* gp120, gp160

**Species (MHC)** macaque**References** Shiver *et al.* 1997

- DNA vaccinations of Rhesus monkeys with a gp120 or gp160 DNA vaccine elicited a strong CD8 cytotoxic T cell response.

**HXB2 Location** Env**Author Location** gp160**Epitope****Immunogen** HIV-1 infection**Species (MHC)** macaque**References** Kent *et al.* 1997b

- Macaques can be infected with HIV, and clear the infection within 6 months, so it is of interest to examine their initial immune response.
- A strong CTL response against env, pol and gag antigens can be detected.
- The CTL response peaked by 4 weeks and declined dramatically by 8 weeks.
- The response in the lymph nodes and peripheral blood was comparable.

**HXB2 Location** Env**Author Location** gp160**Epitope****Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12

**Species (MHC)** mouse**References** Kim *et al.* 1997c

- A gag/pol, vif or env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice.
- When IL-12 was present, CTL response could be detected even without *in vitro* stimulation.

**HXB2 Location** Env**Author Location** gp160**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12

**Species (MHC)** mouse

**References** Kim *et al.* 1997d

- A gag/pol or env DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules CD86, gave a dramatic increase in both the cytotoxic and proliferative responses in mice.
- When CD86 was present, CTL response could be detected even without *in vitro* stimulation.

**HXB2 Location** Env

**Author Location** gp120 (HXBc2)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA prime with gp160 boost  
*Strain:* B clade HXBc2 *HIV component:* gp160

**Species (MHC)** macaque

**References** Letvin *et al.* 1997

- Vaccination of Macaques mulatta (Rhesus monkeys) with an HXBc2 env DNA prime and a protein boost elicited a T cell proliferative response, a CTL response, and type-specific neutralizing antibodies.
- Vaccinated animals challenged with SHIV-HXB2 were protected from infection.

**HXB2 Location** Env

**Author Location** gp120 (MN)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade MN  
*HIV component:* Env, Rev

**Species (MHC)** human

**References** MacGregor *et al.* 1998

- An HIV DNA env and rev vaccine given to 15 asymptomatic HIV+ individuals at three different dosages, 30, 100 or 300 ug, was safe.
- The CTL response to gp120 was enhanced in 0/4 patients in the 30 µg group, 2/3 patients in the 100 µg group, and 0/3 in the 300 µg group – but the non-responding patients in the 300 µg group had a strong CTL response prior to vaccination, and the CTL results are inconclusive.

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Trickett *et al.* 1998

- Twelve HIV-1 infected patients were re-infused with their own lymphocytes, cryopreserved from an earlier time point in the infection.
- Improvement in CD4+ and CD8+ T cells was seen in 7/12, and an increase in the CTL response to Env was seen in one patient.

**HXB2 Location** Env

**Author Location** gp120 (LAI)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Legrand *et al.* 1997

- Seventeen recently infected patients were tested for CTL response to HIV proteins Env, Gag, Pol, Rev, Nef, Vif and Tat.
- An early response (within a month following PI) was noted in 87% of the subjects to Gag, 75% to Env, and 50% to Nef.
- Early responses to Pol, Rev, Vif and Tat were rare.

**HXB2 Location** Env

**Author Location** gp120 (LAI)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vaccinia prime with gp120 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* gp160

**Species (MHC)** human

**References** Corey *et al.* 1998

- Vaccinia-naive subjects were vaccinated with vaccinia-gp160 LAI and boosted with gp120 SF2, LAI, MN, or 160 MN.
- 26/51 had an anti-Env CTL response, and those that were boosted with gp120 tended to produce Abs that neutralized autologous laboratory strains with some cross-reactivity.

**HXB2 Location** Env

**Author Location** Env (IIIB)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Betts *et al.* 1997

- 6/8 individuals from Zambia infected with C clade virus had CTL that were able to make response to B clade HIV-1 IIIB vaccinia-expressed Gag, Pol and Env proteins.
- A vigorous cross-clade response was not limited to a particular protein, and the level of recognition of different proteins varied among the six patients.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** De Maria *et al.* 1997

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T cell function.
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels.

**HXB2 Location** Env

**Author Location** Env (IIIB)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression

**References** Betts *et al.* 1999

- This study demonstrated an inverse correlation between HIV Type I plasma viral load and CTL activity directed against HIV-1 Pol, and stronger combined effects of Pol- and Env-specific CTL, in long-term survivors (LTS) of HIV-1 infection.

**HXB2 Location** Env

**Author Location** Env (LAI)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Buseyne *et al.* 1998a

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human

**References** Goh *et al.* 1999

- 13/37 exposed uninfected individuals with repeated high-risk sexual exposure had HIV-1 specific CTL against Env, Gag, Pol, or a combination of proteins – CTL activity was correlated with a CCR5 wildtype genotype.
- In this group, the highest CTLp frequencies were directed at Gag, but the most common response was to Env and four individuals had responses to multiple HIV-1 proteins.

**HXB2 Location** Env

**Author Location** Env (LAI, MN)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* canarypox *HIV component:* Gag, gp120, gp41, Nef, Protease, RT

**Species (MHC)** human

**References** Evans *et al.* 1999

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination.

**HXB2 Location** Env

**Author Location** Env (LAI)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost  
*Strain:* B clade LAI *HIV component:* Env, Gag

**Species (MHC)** macaque

**Keywords** Th1, Th2

**References** Kent *et al.* 1998

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T cell immunity than either vaccine alone.

- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env. The T help response happened despite a fall in antibody titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced.

**HXB2 Location** Env

**Author Location** Env (LAI, MN)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease

**Species (MHC)** human

**References** Salmon-Ceron *et al.* 1999

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy, uninfected volunteers.

**HXB2 Location** Env

**Author Location** Env (MN)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86

**Species (MHC)** chimpanzee

**References** Kim *et al.* 1998

- The study explores the use of co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* Semliki-Forest Virus with virus-like particle boost *Strain:* B clade IIIB *HIV component:* Gag, gp120

**Species (MHC)** macaque

**References** Notka *et al.* 1999

- Immunization of SIV Pr56Gag-derived VLPs with HIV-1 gp120 anchored on their surface induced Abs, CTL and Th responses to HIV gp120; priming with the HIV antigens in Semliki-Forest Viruses enhanced the immunological outcome.
- Immunized monkeys challenged with SHIV showed a more rapid reduction of plasma viremia.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human

**References** Akridge *et al.* 1999

- This study suggests that HIV-1-resistance in exposed and uninfected individuals is not only associated with the 32-bp deletion in the HIV-1 co-receptor CCR5, but can be related to HIV-1 specific CTL immunity.



**HXB2 Location** Env  
**Author Location** gp120 (BRU)  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** rate of progression  
**References** Aladdin *et al.* 1999

- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death.

**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HAART, ART  
**References** Aladdin *et al.* 2000

- The administration of IL-2 caused an initial enhancement of CD4 cell counts that was accompanied by a decrease in CTL activity – IL-2 therapy did not reduce initial HIV viral load and viral replication was ultimately enhanced.

**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Jin *et al.* 1998a

- CTL precursor frequencies were determined in HIV-1 infected pregnant women, and higher CTLp frequencies to Pol and SF2 Nef, but not IIIB Nef, were found in non-transmitting mothers than in transmitting mothers – Nef CTL responses have been found in uninfected infants born to HIV+ women (Lazuriaga95);
- Very different CTLp frequencies were observed in env depending on whether IIIB, MN, RF, BK, or SF2 was used as antigen – no association between env specific CTL and transmission was observed.

**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Immunogen** vaccinia  
*Vector/Type:* vaccinia *HIV component:* Env  
**Species (MHC)**  
**Keywords** review  
**References** Zavala *et al.* 2001

- This paper is a review of vaccinia in the context of vaccinia strategies that use different vectors to prime and boost, and emphasizes a unique capacity of vaccinia to very efficiently boost memory T-cell responses.
- HIV is discussed in the context of Gonazalo *et al.* 1999, where a V3 CTL epitope expressed in reFlu was boosted most effectively by vaccinia expressing the full Env.

**HXB2 Location** Env  
**Author Location** Env

**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* ZF1 *HIV component:* complete genome

**Species (MHC)** macaque  
**References** Akahata *et al.* 2000

- Rhesus macaques were vaccinated by i.m. injection with naked plasmid DNA carrying an HIV-1 complete genome vaccine, strain ZF1, with a mutated zinc finger in the nucleocapsid to prevent packaging.
- Env and Gag specific CTL but no antibody responses were induced in 2/4 vaccinated monkeys (MM145 and MM153)
- 2/4 monkeys (MM146 and MM143) produced antibodies against p24 and/or gp160, but no CTL response was detected.
- PBMC from all vaccinated monkeys produced IFN-gamma, in response to HIV-1 gp160, indicating a Th response – this response was 5 times higher in MM145, the animal with the strongest CTL response.
- 4 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM145 and MM153 (with a homologous Env) decreased to near or below the detection limit.
- 6-8 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM146 and MM143 decreased near or below the detection limit.

**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Young *et al.* 2001

- Addition of recombinant rec human IL12 (rhIL12) to cultures increased HIV-specific lysis of HIV-Gag, Pol and gp120 vaccinia expressed antigens (11/15 tested increased lysis by > 5%) if the culture was derived from HIV+ individuals who had CD4 cells/ul > 500.
- 2/10 individuals with <200 CD4 cells/ul, and 3/10 individuals with 200-500 CD4cells/ul, had an increase of >5% upon treatment of the culture with rhIL12, so a few individuals in late stage disease had CD8 cells that maintained responsiveness to rhIL12.

**HXB2 Location** Env  
**Author Location** Env (subtype A, B, D)  
**Epitope**  
**Subtype** A, B, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons  
**References** Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.

- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** vaccine

*Vector/Type:* canarypox, protein *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Env, Gag, Protease *Adjuvant:* MF59

**Species (MHC)** human

**References** AVEG022PT 2001

- Different HIV strains were used for different regions: MN (gp120), LAI (gp120, protease and gag), and SF2 gp120
- 26/42 subjects who received CP vac-env-pro vaccine had a CTL response measured by Cr-release, while only 3/17 who were vaccinated with rec gp120 had a CTL response.
- A combination of a CP vac-env-pro vaccine with rec gp120 gave CD8+ T-cells in 62% of subjects, and NAbs in 91% of subjects.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** White *et al.* 2001

- HIV-specific CTL activity was detected in the female reproductive tract of only 1/3 HIV-infected women who underwent a hysterectomy, although CTL could be identified in the PBMC of all three women.

**HXB2 Location** Env

**Author Location** Env (IIIB)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression

**References** Jin *et al.* 2000a

- The CTL precursor level (CTLp) was measured in long term non-progressors (LTNP) with low viral load using limiting dilution analysis and measuring CTL against Env Gag and Pol expressed in vaccinia in autologous targets.
- LTNPs have high memory CTL numbers and low viral load.

**HXB2 Location** Env

**Author Location** Env (IIIB)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, rate of progression

**References** Jin *et al.* 2000a

- The CTL effector levels (CTLe) were compared in long term non-progressors (LTNP) with low viral load and in patients whose virus was well-suppressed by therapy, using a tetramer assay.

- LTNPs have high memory CTLe numbers and low viral load, while HAART patients had low CTLe numbers and low viral load.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human

**Keywords** review, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 2001

- This is a review that summarizes observations about HIV-specific CTL found in the HIV-1 exposed persistently seronegative (HEPS) population.
- The CTL responses assayed by ELISPOT and by CTL precursor frequencies by limiting dilution analysis indicate that CTL in HEPS individuals tend to be of a lower magnitude than in chronic HIV-1 infections – the responses in HEPS cases are below the level of detection by tetramer assays.
- CD8+ CTL responses tend to be detectable in HEPS subjects only if they are recently exposed, and the response diminishes if exposure is reduced – it is not clear if there is a stable memory population in HEPS cases.
- CD8+ CTL responses in the HEPS population are associated with HIV-1 specific CD4+ T cell responses, assayed by proliferation assays, IL-2 secretion, and ELISPOT, and the authors consider the possibility that HIV-1-specific T-help responses improve the "quality" of the CD8+ response in HEPS individuals relative to HIV-1 infected individuals, who tend to have a poor HIV-1-specific T-help response.
- HIV-1 specific CD8+ CTL responses in HIV-1 infected individuals show reduced levels of perforin, and the T cells may not mature properly, and although similar studies have not been conducted in HEPS individuals this is considered as a possible difference in the CTL immune response in HEPS and HIV-1 infected people.

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Env, Gag, Pol

**Species (MHC)** mouse

**Keywords** review

**References** Nabel 2002

- Env DNA constructs were designed that were codon optimized for human genes, express Env in the absence of the regulatory protein Rev, both increasing Env expression levels, deletions in the cleavage site and in the fusion domain. These constructs increased Ab responses to Env, while not diminishing CTL responses, when injected into mice.
- Removing N-linked glycosylation sites did not alter the humoral or cellular immune responses to this HIV protein, as has been seen in analogous SIV experiments.

**HXB2 Location** Env

**Author Location**

**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human  
**Keywords** HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission  
**References** De Maria *et al.* 1994; Kuhn *et al.* 2002

- 6/24 HIV uninfected infants (ages 15-50 months) born to HIV+ mothers had HIV-1 specific CTL responses to vaccinia-expressed Nef, Gag/Pol, Env.
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Env

**Author Location**

**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human

**Keywords** HAART, ART, HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission, rate of progression  
**References** Kuhn *et al.* 2002; Wasik *et al.* 1999

- In HIV-infected infants HIV-specific, CTL responses were not detectable in cord blood or in PBMC collected shortly after birth and were absent or remained very low in 3 infants with a rapidly progressive disease. For those who progressed more slowly, the HIV-specific CTL activity varied.
- The two infants with high levels of Env peptide-stimulated IL-2 responses had the highest CTLp frequencies.
- Stronger responses were detected after initiation of the antiretroviral therapy.
- Two babies that were not infected though born to HIV+ mothers had detectable though low HIV-specific CTLp responses to Env (1/2), Pol (2/2), Gag (1/2) cord blood and transiently in PBMC after birth.
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Env

**Author Location**

**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission  
**References** Aldhous *et al.* 1994; Kuhn *et al.* 2002

- Six of nine HIV vertically infected infants had HIV-1 specific CTL responses to vaccinia expressed Tat (4/6), Pol (6/6), Env (1/6), or Gag (1/6), but not all responses were detected at all time points.
- Two of eleven babies that were not infected though born to HIV+ mothers had detectable responses Tat (1/2), Pol (2/2), Gag (1/2).
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Env

**Author Location**

**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission  
**References** Kuhn *et al.* 2002; McFarland *et al.* 1994

- Only 9% of HIV+ infants had HIV-specific CTL against Env or Gag in unstimulated PBMC. After CD3 stimulation of PBMC, Gag and Env specific CTL were found in PBMC from 91% and 78% of HIV-infected children, respectively, with high precursor frequencies.
- 2/9 babies that were not infected though born to HIV+ mothers had detectable responses to Env.
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Env

**Author Location**

**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human

**Keywords** epitope processing, escape  
**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.

**HXB2 Location** Env

**Author Location**

**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HAART, ART  
**References** Trabattoni *et al.* 2002

- CD8+ T-cells that were stimulated by HIV-1 Env expressing targets from 25 HIV+ patients receiving ART and 17 ART-naive patients were compared. CTL from the individuals receiving ART showed increased TNFalpha production and a reduction of perforin and granzyme expressing CTL, suggesting a functional defect in ART-treated individuals, and a potential benefit of immunomodulants during therapy.

**HXB2 Location** Env

**Author Location** (HXB2)

**Epitope****Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression**References** Edwards *et al.* 2002

- 96% (26/27) chronically infected HIV-1 infected patients elicited gamma-IFN CD8+ T-cell responses against Gag.
- Nef and/or Pol CTL responses were detected in 86% of the subjects.
- The magnitude and breadth of Gag and p24 T-cell responses correlated with absolute CD4 counts, and inversely correlated with viral load.
- Pol and Int CTL responses correlated positively with absolute CD4+ T-cell count.
- Nef and Env responses did not correlate with either CD4 counts or viral load.

**HXB2 Location** Env**Author Location** Env**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade IIIB*HIV component:* gp160, Rev *Adjuvant:* cationic liposome, GM-CSF, IL-2**Species (MHC)** mouse**Keywords** Th2**References** Ishii *et al.* 2001

- Vaccination route of HIV-1 DNA immunization with gp160 and Rev genes was compared including intranasal (i.n.), intramuscular (i.m.), and topical application of DNA directly on the skin after elimination of keratinocyte layers using a strong adhesive. Topical exposure resulted in high level CTL responses, IFN-gamma and IL-4 production, and delayed type hypersensitivity (DTH). Topical application favored Th2 responses.
- DNA delivered topically with adjuvant-like cationic liposomes gave a stronger response than DNA alone, and co-administration of the DNA vaccine with IL-12 and GM-CSF expression vectors enhanced cytotoxic activity and DTH.

**HXB2 Location** Env**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, dendritic cells**References** Larsson *et al.* 2002b

- Autologous mature dendritic cells with rec vaccinia expressing Gag, Pol, Nef and Env could amplify CD8+ T-cell Eli-spot responses 4-38 fold in five HIV+ patients on successful HAART treatment, relative to autologous monocytes. Some weak responses could only be detected using mature dendritic cells as APCs, and this approach could be useful for detection of low frequency memory cells.

**HXB2 Location** Env**Author Location** (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** immunotherapy**References** Trickett *et al.* 2002

- Conditions were optimized for ex-vivo expansion of CD8+ and CD4+ T-cells with the goal of functional T-cell production for autologous immunotherapy. 10,000-fold expansions were obtained in 14 days with optimized concentrations of IL-2, anti-CD3 and anti-CD28 coated microspheres, and decreasing amounts of serum over the first 8 days.

**HXB2 Location** Env**Author Location** (IIIB)**Epitope****Subtype B****Immunogen** HIV-1 and HCV co-infection**Species (MHC)** human**Keywords** rate of progression**References** Lauer *et al.* 2002

- HIV-1 and HCV immune responses were studied in 22 individuals who were co-infected with HIV-1 and hepatitis C virus (HCV). IFN-gamma production was measured in an Eli-spot assay of CD8+ T-cells using targets expressing either Gag, RT, Env and Nef in a vaccinia construct, or one of seven HCV proteins.
- All 22 patients targeted at least one protein. 20/22 patients recognized RT, 17/22 patients recognized Gag, 13/22 subjects recognized Env and 11/22 patients recognized Nef. Robust CTL activity was independent of disease progression or viral load.
- Despite high HCV viral loads, very few HCV CD8+ T-cell Eli-spot responses were detected. In a control HCV infected person who did not have HIV-1, strong anti-HCV responses were mounted.
- HIV-specific CD4 proliferative responses were detected in 9/17 coinfecting patients, but no HCV responses were detected.

**HXB2 Location** Env**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** responses in children**References** Luzuriaga *et al.* 1995

- 2/3 infants infected in utero had detectable HIV-1 Gag and Env specific CTL responses, one by 4 months, one by 11 months of age. Levels of the responses varied at different time point. Pol responses were not detected.
- 2/4 infants infected intrapartum had detectable responses, one note until 11 months, one not until 42 months.
- HIV-specific CTL were not detected in ten HIV- infants that were born to HIV+ mothers.

**HXB2 Location** Env**Author Location****Epitope****Immunogen** vaccine*Vector/Type:* canarypox prime with gp120*boost HIV component:* Env, Gag**Species (MHC)** human**References** Gupta *et al.* 2002

- A safety and immunogenicity study of a vaccine dosing schedule was studied in a trial conducted in high and low risk study subjects. There was a 76% cumulative probability of detecting a Gag or Env CTL response by day 728.

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, responses in children

**References** Scott *et al.* 2001

- CTL responses before and after initiation of ART were studied in 13 HIV-1 vertically infected infants <6 months of age, and 4 that were >6 months of age.
- Before ART 2/13 infants <6 months of age showed IFN $\gamma$  ELISPOT CD8+ T-cell responses, one to Nef and one to Env and Nef, and these responses became undetectable after successful therapy— 3 infants were coinfecting with CMV and all 3 had CMV-specific CD8+ T-cell responses.
- One older infant, at 23 months, had CTL responses against all for proteins tested, Gag, Pol, Nef and Env, and had the lowest plasma viremia of the study group. 3/4 infants older than 6 months of age responded to either Nef or Pol.
- Administration of ART over 48 weeks broadened the HIV-1-specific CTL response in 2/4 of the older children that were incomplete responders.

**HXB2 Location** Env

**Author Location** (IIB)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Ortiz *et al.* 2001

- Immune responses in eight chronically HIV-1 infected patients undergoing HAART therapy structured treatment interruptions (STI) were studied. STI boosted HIV-1 specific CTL responses and elevated CTL responses were maintained up to 22 weeks after the last treatment interruption, but viral load rebound to pretreatment levels and CD4 T-cell count decline was observed. CD8 responses in PBMC were measured by cytokine flow cytometry with gp160, Gag p55, RT-Pol and Nef expressed in vaccinia.
- One of seven subjects with a detectable NAb response had an augmented neutralization titer in response to STI.

**HXB2 Location** Env

**Author Location** (SF2)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*2402, A\*3303, B\*3501, B\*5101

**Keywords** class I down-regulation by Nef

**References** Tomiyama *et al.* 2002

- Nef down-regulates class I molecules, and the killing activity of HLA B\*3501, A\*2402, B\*5101 and B\*3303-restricted HIV-1-epitope specific CTL clones was inhibited by an HIV-1 strain carrying Nef, relative to a Nef-deleted virus; while Nef-induced HLA class I down-regulation inhibited lysis, it did not abolish cytokine production by HIV-1-specific CD8+ T-cells.

**HXB2 Location** Env

**Author Location** Env (gp160) (IIB)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade NL43

*HIV component:* Env

**Species (MHC)** macaque

**References** Akahata *et al.* 2003

- Four monkeys were injected i.m. with a SHIV plasmid (SHIV-NM-3rn ZF1\*) which encodes all viral proteins driven by the SIV LTR promoter. Infectivity is prevented by the introduction of mutations within the zinc-finger motifs of the nucleocapsid (NC) that prevents RNA packaging. An original NC ZF1 mutant plasmid was constructed using NL43 (Akahata 275:116-124 (2000) – the SHIV construct was made as an alternative to get improved expression in macaques using an SIV promoter. CTL were detected by lysis of HIV-1 Env IIB or SIV Gag mac239 expressing target cells, and a T cell proliferative response to Env was observed. Env-directed antibodies were detected by ELISA. All vaccinated macaques had a low peak viral loads that fell below the level of detection within 6 weeks post-challenge with autologous SHIV SHIV-NM-3rn.

**HXB2 Location** Env

**Author Location** Env (MN)

**Epitope**

**Subtype** B

**Immunogen** SIV infection, SHIV infection

**Species (MHC)** macaque

**Assay type** CD8 T-cell ELISPOT - IFN $\gamma$

**Keywords** assay standardization/improvement

**References** Calarota *et al.* 2003

- The sensitivity of gamma INF ELISPOT assays can be enhanced for the detection of low frequency responses, like after ART, by adding IL-15 to the assay.
- CD8+ T-cells from SHIV and SIV infected macaques with peptide pools from Gag and Env were used to test this system.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Subtype** multiple

**Immunogen**

**Species (MHC)** human

**Assay type** Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Currier *et al.* 2003

- CD8-cellular immune responses from 21 HIV-1 infected patients from Kenya infected with subtype A, C, D, and unique recombinants were studied for cross-recognition of Gag, Env, and Nef vaccinia-expressed proteins representing subtypes A-H, including CRF01.
- Both subtype-specific and cross-reactive CTL were observed, with a skewing of responses towards the infecting subtype in the nine subjects with full length sequence available. The magnitude of the responses to Gag were the highest, less to Nef, and still less to Env.
- For Gag, 8/21 subjects responded to at least 7/8 different subtype proteins, 7 had a mixed response, recognizing some subtypes but not others, and 6 responded to only one or none of the different subtype proteins. For Env, 4/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 7 responded to one or none. For Nef, 5/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 6 responded to one or none.

**HXB2 Location** Env**Author Location** Env (HIV-1 IIIB)**Epitope****Immunogen** HIV-1 exposed seronegative**Species (MHC)** human**Assay type** Cytokine production**Keywords** HIV exposed persistently seronegative (HEPS)**References** Fowke *et al.* 2000

- A cohort of Nairobi sex-workers were defined as resistant to HIV-infection by virtue of remaining seronegative despite repeated high risk exposures. 24 were tested for HIV specific T-helper responses determined by IL-2 production *in vitro* in response to gp120 peptides or soluble gp120 protein.
- 7/17 resistant women showed IL-2 stimulation which was greater than or equal to 2.0, and specific CTL responses were detected in 15/22 resistant women as compared to 0/12 of the control low-risk subjects.

**HXB2 Location** Env**Author Location** gp160 (MN)**Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade MN*HIV component:* gp160 *Adjuvant:* IL-12**Species (MHC)** mouse**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** adjuvant comparison**References** Chattergoon *et al.* 2004

- pIL-12 used as adjuvant significantly increases the number of Ag-specific CD8+ T-cells and a sustained memory response. Also, the splenocytes from mice that received pIL-12 were shown to proliferate to a much higher extent. Mice immunized with a plasmid expressing the influenza A/PR8/34 HA gene and pIL-12 were better able to control the infection.

**HXB2 Location** Env**Author Location** Env**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay**Keywords** HAART, ART, immune dysfunction**References** Trabattoni *et al.* 2004

- Reduced perforin-and granzyme- containing Env-specific CD8+ T cells were observed in ART treated individuals indicating that antiretroviral drugs might directly interfere with the production of perforin and granzymes, inhibiting CTL killing. Immunomodulants may be needed to enable CTL to become fully functional during ART.

**HXB2 Location** Env**Author Location** gp140**Epitope****Immunogen** vaccine*Vector/Type:* protein, peptide in liposome*Strain:* B clade IIIB *HIV component:*gp140, gp160, oligomeric gp140 *Adjuvant:*

CpG immunostimulatory sequence (ISS), liposome

**Species (MHC)** mouse**Donor MHC** H-2d**Assay type** Cytokine production, proliferation, Chromium-release assay**Keywords** Th1, Th2, adjuvant comparison, vaccine antigen design**References** Rao *et al.* 2004

- Administration of ogp140 in liposomes containing lipid A (LA) induces high antibody titers which are increased by adding CpG ODN. Priming and boosting of BALB/c mice with ogp140+LA induces mixed Th1/Th2 immune response, while adding CpG ODN switches the immune response to a Th1 type. Mixing ogp140 with liposomes containing lipid A yielded excellent proliferative and CTL specific responses; CpG did not affect CTL responses. The antigen did not need to be encapsulated in the liposome to induce strong responses with LA as an adjuvant.

**HXB2 Location** Env**Author Location****Epitope****Subtype** CRF02\_AG**Immunogen** vaccine*Vector/Type:* virus-like particle (VLP), DNA

prime with modified vaccinia Ankara (MVA)

boost *Strain:* CRF02 IC0928 *HIV component:*

Env, Gag, Pol

**Species (MHC)** macaque**Assay type** T-cell Elispot, Intracellular cytokine staining**Keywords** vaccine-specific epitope characteristics, vaccine antigen design**References** Ellenberger *et al.* 2005

- Macaques were given a Gag-Pol-Env DNA prime followed by an MVA boost. Two DNA constructs were compared, one that resulted in mature VLPs with processed Gag (IC48) and one that had a point mutation in Gag that resulted in immature VLPs (IC1-90). IC48 DNA vaccinations, which produced

mature VLPs, yielded 2-fold stronger T-cell responses with greater breadth. CD4 T-cells responded to 3-fold more peptide pools than did CD8.

- HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** CRF02\_AG  
**Immunogen** vaccine  
*Vector/Type:* virus-like particle (VLP), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* CRF02 IC0928 *HIV component:* Env, Gag, Pol
- Species (MHC)** macaque  
**Assay type** T-cell Elispot, Intracellular cytokine staining  
**Keywords** vaccine-specific epitope characteristics, vaccine antigen design  
**References** Ellenberger *et al.* 2005
- Macaques were given a Gag-Pol-Env DNA prime followed by an MVA boost. Two DNA constructs were compared, one that resulted in mature VLPs with processed Gag (IC48) and one that had a point mutation in Gag that resulted in immature VLPs (IC1-90). IC48 DNA vaccinations, which produced mature VLPs, yielded 2-fold stronger T-cell responses with greater breadth. CD4 T-cells responded to 3-fold more peptide pools than did CD8.

- HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* Other *HIV component:* Env, Gag, Pol, Rev, Tat, Vif, Vpr
- Species (MHC)** macaque  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** vaccine-specific epitope characteristics, vaccine antigen design  
**References** Sadagopal *et al.* 2005
- 22/23 macaques that were immunized with a DNA prime SHIV-89.6 and boosted with rMVA showed successful control of viremia, with low or undetectable viral loads and normal CD4 counts 200 weeks postchallenge. IFN-gamma producing T cells were found in unexpectedly low breadths and frequencies. T-cell responses were stable over time and maintained their production of IFN-gamma and IL-2. Long-term control was found in macaques of diverse histocompatibility types. The CD8 T cells seemed to have the most impact on well-contained chronic infections in the vaccinated and challenged animals.
  - Both CD4 and CD8 responses were found to the SIV Gag and HIV Env proteins; 60% of CD8+ epitopes and 80% of CD4+ epitopes were in p27.

**HXB2 Location** Env  
**Author Location**  
**Epitope**

**Immunogen** vaccine  
*Vector/Type:* DNA prime with vaccinia boost, DNA, Other *Strain:* Other *HIV component:* Env, Gag

- Species (MHC)** mouse  
**Assay type** T-cell Elispot  
**Keywords** vaccine-induced epitopes, vaccine antigen design  
**References** Xu *et al.* 2006
- Sequential cross-clade vaccination strategy was tested in BALB/c and C57BL/6 mice. Vaccines used were C/B recombinant strain (CN54), B strain (RL42), A/E recombinant strain (AE2F).
  - Sequential priming and boosting with heterologous HIV immunogens stimulated T cell immunity against conserved epitopes, while a single vaccine derived from one clade or the mixture of multiple vaccines from different clades raised T cells against less conservative or non-conservative epitopes.

**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA with CMV promotor *Strain:* B clade HXB2, B clade NL43, A clade 92RW020, C clade 97ZA012 *HIV component:* Env, Gag, Nef, Pol

- Species (MHC)** human  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** therapeutic vaccine  
**References** Catanzaro *et al.* 2006

- 14 volunteers uninfected with HIV completed a set of injections with a 6-plasmid DNA vaccine encoding EnvA, EnvB, EnvC, and subtype B Gag, Pol, and Nef. CD4 and CD8 T cell responses to Env and Gag were most frequently detected.
- For EnvA, 2/14 subjects showed a positive CD8+ T cell response by ICS.

**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* adenovirus type 5 (Ad5) *HIV component:* Env, Gag *Adjuvant:* Cholera toxin (CT)

- Species (MHC)** macaque  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** vaccine antigen design  
**References** Mercier *et al.* 2007

- 3 rhesus macaques were given oral immunizations with an enteric-coated mixture of adenoviral vectors expressing HIV-1 gag and a string of conserved env peptides representing broadly cross-reactive CD4+ and CD8+ epitopes. The macaques were boosted intranasally with a mixture of 6 HIV-1 envelope peptides plus cholera toxin adjuvant.

- The immunizations increased cellular immune responses, including antigen-specific IFN $\gamma$ -producing CD4+ and CD8+ effector memory T cells in the intestine. After only the oral immunization, there were no EliSpot responses to env peptides or to gag. After the intranasal boost, EliSpot responses against env peptides and against inactivated HIV were markedly increased, but gag responses were not.

**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** C  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* Other, C clade consensus *HIV component:* Env

- Species (MHC)** guinea pig, mouse  
**Assay type** T-cell Elispot  
**Keywords** vaccine antigen design  
**References** Kothe *et al.* 2006
- Ancestral and consensus subtype C sequences were tested for immunogenicity. Both AncC and ConC env genes expressed functional Env glycoproteins that were immunogenic in laboratory animals and elicited humoral and cellular immune responses of comparable breadth and magnitude.
  - Mice immunized with C-ancestral, C-consensus, and 96ZM651.8-opt env plasmids all elicited IFN-g EliSpot T cell responses at similar levels.

**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with vaccinia boost  
*Strain:* B clade JRFL, A clade 92RW020, M group Consensus, C clade 96ZM651 *HIV component:* Env

- Species (MHC)** mouse  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** variant cross-recognition or cross-neutralization, vaccine antigen design  
**References** Weaver *et al.* 2006
- 3 different mouse strains were immunized with subtype A, B, C, and M-group consensus env DNA immunogens. CTL and Helper T-cell epitopes were mapped using peptide sets from heterologous A, B, and C viruses. The consensus immunogen induced a greater number and magnitude of T-cell responses than any single wild-type env.

**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade

**Species (MHC)** macaque  
**Assay type** Intracellular cytokine staining  
**Keywords** subtype comparisons, vaccine antigen design  
**References** Smith *et al.* 2005

- Macaques were immunized with a clade B HIV vaccine and tested for responses to pools of clade B and A/G Env and Gag peptides. While CD4 responses were more frequent than CD8 responses, higher cross-clade responses were found for CD8 responses. The authors suggest that the better cross-clade reactivity of the CD8 responses reflects the size difference between CD8 and CD4 epitopes; the smaller CD8 epitopes provide a smaller target for mutation.
- For both B and A/G Env and Gag peptides, 3/5 pools produced CD8+ T cells, suggesting the existence of 2 or 3 cross-reactive CD8 epitopes.

## II-B-23 Nef CTL/CD8+ epitopes

**HXB2 Location** Nef (1–15)  
**Author Location** Nef  
**Epitope** MGGKWSKRSVVGWPT  
**Epitope name** nef-5139  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)  
**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism  
**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, MGGKWSKRSVVGWPT was mutated in the daughter D2 isolate to MGGKWSKsSiVG-WPa.

**HXB2 Location** Nef (1–16)  
**Author Location** Nef (1–16)  
**Epitope** MGGKWSKSSIVGWPAV  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human



**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Nef (3–11)

**Author Location** Nef (3–)

**Epitope** GKWSKSSIV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian subclade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope GKWSKSSIV, is predicted to bind HLA-A2 with a binding affinity score of 236.732.

**HXB2 Location** Nef (5–13)

**Author Location** Nef (5–13 HXB2)

**Epitope** WSKSSIIGW

**Epitope name** WW9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*2501)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- This is a newly defined epitope. Positions 4 and 6 in the epitope had potentially experienced positive selection. WSKtSIIGW and WSKSSmIGW escape variants were found.

**HXB2 Location** Nef (5–19)

**Author Location** Nef

**Epitope** WSKRSVVGWPTVRER

**Epitope name** nef-5140

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, WSKRSVVGWPTVRER was mutated in the daughter D2 isolate to WSKsSiVGWPaVRdR.

**HXB2 Location** Nef (9–23)

**Author Location** Nef

**Epitope** SVVGWPTVRERMRR

**Epitope name** nef-5141

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.

- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, SVVGWPTVRERMRA was mutated in the daughter D2 isolate to SiVGWPaVRdRMRA.

**HXB2 Location** Nef (9–23)  
**Author Location** Nef (9–23)  
**Epitope** SVVGWPAVRERMRA  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A23, B62  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** computational epitope prediction, vaccine-induced epitopes  
**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- SVVGWPaVRERMRA is a previously unpublished epitope that varies from the consensus at position 7.

**HXB2 Location** Nef (11–20)  
**Author Location** Nef  
**Epitope** VEWPAVRERM  
**Epitope name** VM10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A28, A29, B14, B44, Cw8  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 2, VgWPAVRERM, was found not to correspond to the most polymorphic residue in the epitope. This is a novel unmapped epitope.

**HXB2 Location** Nef (13–20)

**Author Location** Nef (13–20 LAI)  
**Epitope** WPTVRERM  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008; Goulder *et al.* 1997g

- C. Brander notes this is a B\*0801 epitope.

**HXB2 Location** Nef (13–20)  
**Author Location** Nef (HXB2)  
**Epitope** WPTVRERM  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** (B\*0801)  
**Keywords** class I down-regulation by Nef  
**References** Peng & Robert-Guroff 2001

- Deletion of the 19 N-terminal amino acids from Nef including the myristolation signal eliminates Nef-induced down-regulation of MHC class I and CD4 molecules. Such a construct has the potential to serve as a more potent immunogen. The known T-cell epitopes that that would be disputed by this deletion are minimal, including the HLA-B8 CTL epitope WPTVRERM.

**HXB2 Location** Nef (13–20)  
**Author Location** (C consensus)  
**Epitope** WPAIRERM  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Nef (13–20)  
**Author Location** Nef  
**Epitope** WPTVRERM  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0801)  
**Donor MHC** A\*0101, B\*0801  
**Country** United Kingdom  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** escape, acute/early infection  
**References** Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- The recipient mounted an acute CTL response to this epitope, and the escape variant wpAvrKrm emerged in the recipient soon after.

**HXB2 Location** Nef (13–20)

**Author Location** (C consensus)

**Epitope** WPAIRERM

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- WPAIRERM is an optimal epitope.

**HXB2 Location** Nef (13–20)

**Author Location** Nef (13–20)

**Epitope** WPTVRERM

**Epitope name** WM8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- A CON peptide, WPTVRERMRRRAEPAA contained the epitope WPTVRERM (WM8) and elicited a IFN-gamma immune response.

**HXB2 Location** Nef (13–20)

**Author Location** Nef (13–20 LAI)

**Epitope** WPTVRERM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Goulder *et al.* 1997g

- Unusual epitope for HLA-B8, but compatible with crystal structure predictions.

**HXB2 Location** Nef (13–20)

**Author Location** Nef (13–20)

**Epitope** WPTVRERM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the HLA A2+ was HLA A\*0201, A31, B8, B51 and responded to this epitope as well as seven others.

**HXB2 Location** Nef (13–20)

**Author Location** Nef (13–20 SF2)

**Epitope** WPTVRERM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 1/3 group 1, 0/3 group 2, and 1/2 group 3.

**HXB2 Location** Nef (13–20)

**Author Location** Nef (13–20)

**Epitope** WPTVRERM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.

**HXB2 Location** Nef (13–20)

**Author Location** Nef (13–20)

**Epitope** WPTVRERM

**Epitope name** WM8

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A\*03, A\*31, B\*08, B\*15, Cw\*04, Cw\*07

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion

**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- The variant WnTVRERM was present in 10/10 clones from a B8+ mother, was transmitted to her B8- infant, and present in 10/10 clones at months 2, 4, and 15.

**HXB2 Location** Nef (13–20)

**Author Location** Nef

**Epitope** WPTVRERM

**Epitope name** B8-WM8(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (13–20)

**Author Location**

**Epitope** WPTVRERM

**Immunogen**

**Species (MHC)** (B8)

**Keywords** review, immunodominance, escape, vaccine antigen design

**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection.

**HXB2 Location** Nef (13–27)

**Author Location** Nef

**Epitope** WPTVRERMRAEPAA

**Epitope name** nef-5142

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, WPTVRERMRAEPAA was mutated in the daughter D2 isolate to WPaVRdRMR-RAEPAA.

**HXB2 Location** Nef (15–23)

**Author Location** Nef (15–)

**Epitope** AVRERMRRRT

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7, B8)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope AVRERMRRRT, is predicted to bind HLAs - B7 and B8 with binding affinity scores of 15 and 6.

**HXB2 Location** Nef (15–23)

**Author Location** Nef (15–23)

**Epitope** TVRERMRRRA

**Subtype** B

**Immunogen** HIV-1 infection, peptide-HLA interaction  
**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** immunodominance

**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, TVRERMRRRA, is similar to human protein Rhomboid protein, sequence TTVRsRMRRRA.

**HXB2 Location** Nef (19–27)

**Author Location** Nef (19–27)

**Epitope** RMRRAEPAA

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Nef (19–27)

**Author Location** Nef (19–27)

**Epitope** RMRRAEPAA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Donor MHC** 1261: A\*0201, A29, B58, B62, Cw\*0304, Cw\*1601

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes was characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** Nef (22–30)

**Author Location** Nef (22–30)

**Epitope** RAEPAADGV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6901)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope RAEPAADGV showed >20% conservation to subtype B.

**HXB2 Location** Nef (22–30)

**Author Location** Nef (22–)

**Epitope** RTEPAAEGF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope RTEPAAEGF, is predicted to bind HLA-A1 with a binding affinity score of 22.5.

**HXB2 Location** Nef (29–37)

**Author Location** Rev (29–37)

**Epitope** GVGAVSRDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, GVGAVSRDL, was detected within overlapping peptides DVGAVSRDLEKHGAI and RRAEPAADGVGAVSRDL.

**HXB2 Location** Nef (29–37)

**Author Location** Nef (29–)

**Epitope** VGGAASQDL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205, B7)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope VGGAASQDL, is predicted to bind HLAs A\*0205 and B7 with binding affinity scores of 14 and 20.

**HXB2 Location** Nef (29–37)

**Author Location** Nef (29–37)

**Epitope** VGGAASRDLD

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6901)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.

- Epitope VGGAASRDLD showed >20% conservation to subtypes B and D.

**HXB2 Location** Nef (29–43)

**Author Location** Nef (29–43)

**Epitope** GVGAVSRDLEKHGAI

**Epitope name** GI-15 or Nef8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** rate of progression, acute/early infection, memory cells

**References** Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to peptide GI-15, IFN-gamma and IL-2 were produced by CD127 hi cells in patients given early ART. TNF-alpha was secreted by CD127 lo cells. Longitudinally, in one patient, IFN-gamma was secreted by both CD127 hi and lo cells before treatment but was maintained in CD127 hi cells after treatment. CD127 hi cells were responsible for producing IL-2 and TNF-alpha after ART.

**HXB2 Location** Nef (32–46)

**Author Location** Nef (32–46)

**Epitope** AVSRDLERHGAISS

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide AVSRDLERHGAISS is a previously unpublished epitope that varies from the consensus at position 8.

**HXB2 Location** Nef (37–45)

**Author Location** Nef (37–45)

**Epitope** LEKHGAITS

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4001)

- Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- HXB2 Location** Nef (37–45)  
**Author Location** Nef (37–45)  
**Epitope** LEKHGAITS  
**Immunogen**  
**Species (MHC)** human (B50)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008
- HXB2 Location** Nef (37–45)  
**Author Location** Nef (37–45)  
**Epitope** LEKHGAITS  
**Epitope name** LS9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B4001, B50)  
**Donor MHC** A\*0201, A\*2402, B\*4001, B\*5001, Cw03, Cw04  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization  
**References** Draenert *et al.* 2006
- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
  - This epitope, LEKHGAITS (LS9) was restricted by HLA-B50/B\*4001. Variants that arose were LdKHGAITS and LEKHGAITS.
- HXB2 Location** Nef (42–50)  
**Author Location** Nef (44–52 HXB3)  
**Epitope** ALTSSNTAA  
**Immunogen** vaccine  
*Vector/Type:* DNA, peptide *Strain:* B clade HXB3 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (A\*0201)  
**Keywords** binding affinity, computational epitope prediction  
**References** Sandberg *et al.* 2000
- Ten Nef 9-mer peptides were predicted to have a strong binding affinity with HLA-A\*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly.
  - A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with either nef DNA under the control of a CMV promoter, coated on gold particles delivered to abdominal skin by gene gun.
- ALTSSNTAA was also tested by subcutaneous injection of Nef peptides in Freund's adjuvant.
  - ALTSSNTAA bound weakly to HLA-A2, but it had the strongest CTL response among the three elicited by the DNA vaccine and a strong response to the peptide vaccination.
- HXB2 Location** Nef (42–50)  
**Author Location** Nef (42–)  
**Epitope** ALTSSNTDT  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons  
**References** Kumar *et al.* 2006a
- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
  - Of the most common HLA in India tested, this epitope ALTSSNTDT, is predicted to bind HLA-A\*0201 with a binding affinity score of 7.452.
- HXB2 Location** Nef (42–50)  
**Author Location** Nef (42–50)  
**Epitope** ALTSSNTAA  
**Epitope name** Nef42-50  
**Immunogen** HIV-1 infection  
**Species (MHC)** human, humanized mouse (A2)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** responses in children, immunodominance, characterizing CD8+ T cells  
**References** Chandwani *et al.* 2004
- Responses to five HLA-A2 presented epitopes in Nef were characterized in a population of 19 HIV infected adults and 21 children. The CD8 T-cell response to Nef was stronger and broader in adults than children, averaging 652 and 87 SFCs/10<sup>6</sup> PBMC, and 2.6 and 0.9 recognized epitopes per person, respectively.
  - This is one of three novel Nef epitopes previously identified in HLA-A2 transgenic mice, shown to induce CD8 T-cell response in humans. It was not the immunodominant response.
- HXB2 Location** Nef (48–56)  
**Author Location** Nef (58–66 JRFL)  
**Epitope** TAATNADCA  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade JRFL  
**Species (MHC)** mouse (H-2<sup>b</sup>)  
**References** Liang *et al.* 2002
- BALB/c, C3H/HeN and C57BL/6 mice were given intramuscular immunization with Nef DNA constructs – C57BL/6 responded to this epitope.

- The Nef mutant that lacked the myristylation site (G→A) at position 2, and the dileucine motif (L → A at positions 174 and 175) was impaired in terms of its ability to elicit induction of Nef-specific CD4+ and CD8+ T-cell responses. The myristylation site is critical for Nef membrane localization and function, and the di-leucine motif for the down-regulation of surface CD4 molecules, and the mutation of these regions could yield a safer vaccine.
- N-terminal addition of human tissue plasminogen activator (TPA) to Nef, enhanced CD8+ T-cell responses and could compensate for the G2A, L174A, L175A mutations – this enhanced immunogenicity correlated with enhanced levels of protein expression in transfected cells.

**HXB2 Location** Nef (50–58)

**Author Location** Nef (50–)

**Epitope** ATNADCAWL

**Epitope name** Nef50

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* Nef  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This peptide was a low A2-binder that did not induce CTL or CD8+ T-cell IFN gamma responses in mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.

**HXB2 Location** Nef (52–60)

**Author Location** Nef (52–)

**Epitope** NADCAWLRA

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope NADCAWLRA, is predicted to bind HLA-A1 with a binding affinity score of 2.5.

**HXB2 Location** Nef (58–66)

**Author Location** Nef (56–)

**Epitope** LQAQEEEDV

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope, LQAQEEEDV, is predicted to associate with 40% of them.

**HXB2 Location** Nef (62–81)

**Author Location** Nef (61–80)

**Epitope** EEEVGFVPVTPQVPLRPMTY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** Nef (62–81)

**Author Location** Nef (61–80 SF2)

**Epitope** EEEVGFVPVTPQVPLRPMTY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Twelve subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Two of these 12 had CTL response to this peptide.
- The responding subjects were HLA-A11, A24, B8, B35, and HLA not determined.

**HXB2 Location** Nef (62–81)

**Author Location** Nef (61–80 SF2)

**Epitope** EEEVGFVTPQVPLRPMTY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** Nef (62–81)

**Author Location** Nef (SF2)

**Epitope** EEEVGFVPVTPQVPLRPMTY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.



- Nef peptides PQVPLRRMTYKAAVDLSHFL, KAAVDLSHFLKEKGGLEGLI and EEEVGFPVTPQVPLRPMTY were recognized and the first two share KAAVDLSHFL (a Cw8 epitope), the first and last share PQVPLRPMTY.

**HXB2 Location** Nef (63–77)

**Author Location** Nef (63–77)

**Epitope** EEEVGFPVKPQVPLR

**Epitope name** FL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, EEEVGFPVKPQVPLR, varies at position 9 from the consensus.

**HXB2 Location** Nef (64–74)

**Author Location** Nef (C consensus)

**Epitope** GEVGFVPRPQV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B45)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, viral fitness and reversion

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- People who carried B45 tended to carry a variant of this epitope, while people who did not almost always carried the consensus form.
- B\*4501 was one of the HLA types associated with having a high viral load.

**HXB2 Location** Nef (65–82)

**Author Location** Nef

**Epitope** EVGFVPRPQVPLRPMTYK

**Epitope name** NEF-10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, EVGFVPRPQVPLRPMTYK differs from the consensus C sequence EVGFVPRPQVPLRPMTfK at 1 amino acid position, i.e. by 5.6%.

**HXB2 Location** Nef (65–82)

**Author Location** Nef

**Epitope** EVGFVPRPQVPLRPMTYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved

peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- EVGFVPRPQVPLRPMTYK is the most frequently targeted across ethnicities. It is immunodominant, and had an overall frequency of recognition of 44.7% - 52.5% AA, 50% C, 34.1% H, 38.1% WI. This peptide is included in a 58 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region I', EVGFVPRPQVPLRPMTYKAAVDLSHFLKEKGGLEGLIYSQK, a 41 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** Nef (66–74)

**Author Location** Nef (67–)

**Epitope** VGFPVPRPQV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope VGFPVPRPQV, is predicted to bind HLA-A\*0201 with a binding affinity score of 2.856.

**HXB2 Location** Nef (66–80)

**Author Location** Nef (66–80 BRU)

**Epitope** VGFPVTPQVPLRMT

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1, B8)

**References** Hadida *et al.* 1992

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients.

**HXB2 Location** Nef (66–80)

**Author Location** Nef (64–78)

**Epitope** VGFPVTPQVPLRMT

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1, B8)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** Nef (66–97)

**Author Location** Nef (66–97 LAI)

**Epitope** VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGG

### Subtype B

**Immunogen** vaccine

*Vector/Type:* lipopeptide

**Species (MHC)** human

**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 5/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual.
- 5/12 tested had an IgG response to this peptide.

**HXB2 Location** Nef (67–81)

**Author Location** Nef (67–81)

**Epitope** GFPVPRPQVPLRPMTY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Nef (68–76)

**Author Location** Nef (68–76)

**Epitope** FPVKPQVPL

**Epitope name** FL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07, B\*35)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- A PTE-B peptide, EEEVGFPVkpQVPLR containing the epitope FPVPRPQVPLR (FL10) was found in two subjects and elicited an IFN-gamma immune response.

**HXB2 Location** Nef (68–76)

**Author Location** Nef (68–76)

**Epitope** FPVTPQVPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Nef (68–76)  
**Author Location** Nef (103–111)  
**Epitope** FPVRPQVPL  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702)  
**Assay type** Other  
**Keywords** HLA associated polymorphism  
**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- FPVRPQVPL was a previously defined B\*0702 presented epitope that encompassed a B\*07 associated polymorphism, FPVrPQVPL, in the fourth position.

**HXB2 Location** Nef (68–76)  
**Author Location** Nef (68–76)  
**Epitope** FPVRPQVPL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*35)  
**Donor MHC** A\*03, A\*24, B\*35, B\*40  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** acute/early infection, variant cross-recognition or cross-neutralization, superinfection  
**References** Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- This epitope FPVRPQVPL was identical in the initial and superinfecting strains, and the CTL response persisted in the patient before and after superinfection.

**HXB2 Location** Nef (68–76)  
**Author Location** Nef (72–80 SF2)  
**Epitope** FPVRPQVPL  
**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)  
**References** Tomiyama *et al.* 1997

- A CTL clone responsive to this epitope was obtained.
- 3/7 B35-positive individuals had a CTL response to this epitope.
- An R to T substitution at position 4 abrogates specific lysis, but not binding to B\*3501.

**HXB2 Location** Nef (68–76)  
**Author Location** Nef (72–80)  
**Epitope** FPVRPQVPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**References** Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B\*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

**HXB2 Location** Nef (68–76)  
**Author Location** Nef (68–76)  
**Epitope** FPVRPQVPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding  
**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

- References** Reche *et al.* 2006
- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naïve individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
  - A more detailed evaluation of HIV-naïve T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
  - This epitope, FPVRPQVPL, was predicted to be restricted by HLA A\*2902, B\*0702, B\*3501, B\*5101, B\*5102, B\*5103, B\*5301 and B\*5401.

**HXB2 Location** Nef (68–76)  
**Author Location** Nef (72–80 SF2)  
**Epitope** FPVRPQVPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**References** Shiga *et al.* 1996

- Binds HLA-B\*3501.

**HXB2 Location** Nef (68–76)

**Author Location** (SF2)

**Epitope** FPVRPQVPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** rate of progression

**References** Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals, but this was one of the six that had no B35 associated pattern of mutation.

**HXB2 Location** Nef (68–76)

**Author Location** Nef (66–74)

**Epitope** FPVRPQVPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** Nef (68–76)

**Author Location** Nef (68–76 BRU)

**Epitope** FPVTPQVPL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** binding affinity, epitope processing

**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- FPVTPQVPL was recognized in 1/13 (8%) of individuals with HLA B7, and 1/12 (8%) of individuals with HLA B35. It was a high affinity HLA binder.

**HXB2 Location** Nef (68–76)

**Author Location** Nef (68–76)

**Epitope** FPVTPQVPL

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (B7)

**Keywords** binding affinity, dendritic cells, Th1

**References** Wilson *et al.* 1999b

- Dendritic cells are the most potent for priming T cell responses – DCs can stimulate autologous CTL responses from T cells cultured from HIV negative donors.

- Th1-biasing cytokines IL-12 or IFN alpha enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within.

- B7 and A2 Nef epitopes were studied – FPVTPQVPL has a high affinity for B7.

**HXB2 Location** Nef (68–76)

**Author Location** Nef (68–76)

**Epitope** FPVTPQVPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconverter homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

**HXB2 Location** Nef (68–76)

**Author Location** Nef (68–76 BRU)

**Epitope** FPVTPQVPL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** binding affinity, epitope processing

**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- FPVTPQVPL was recognized in 1/13 (8%) of individuals with HLA B7, and 1/12 of individuals with HLA B35. It was a high affinity HLA binder.

**HXB2 Location** Nef (68–76)

**Author Location** Nef (68–76)

**Epitope** FPVTPQVPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. Also, none of 4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Nef (68–76)

**Author Location** Nef (68–76)

**Epitope** FPVTPQVPL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (B7 supertype)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** Nef (68–76)

**Author Location** Nef (69–)

**Epitope** FPVRPQVPL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7, Cw\*0401)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope FPVRPQVPL, is predicted to bind HLAs - B7 and Cw\*0401 with binding affinity scores of 80 and 120.

**HXB2 Location** Nef (68–77)

**Author Location** Nef (68–77)

**Epitope** FPVRPQVPLR

**Epitope name** FR10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- A CON peptide, EVGFPVRPQVPLR contained the epitope FPVRPQVPLR (FL10) and elicited an IFN-gamma immune response.

**HXB2 Location** Nef (68–77)

**Author Location** Nef (68–77 LAI)

**Epitope** FPVTPQVPLR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0702 epitope.

**HXB2 Location** Nef (68–77)

**Author Location** Nef (68–77 LAI)

**Epitope** FPVTPQVPLR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Haas *et al.* 1996

- There was a high degree of variation in three CTL epitopes in Nef in four slow and non-progressors, and variant specific CTLs arose over time to eliminate variants, indicating immune selection.

**HXB2 Location** Nef (68–77)

**Author Location** Nef (subtype B)

**Epitope** FPVTPQVPLR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** HIV exposed persistently seronegative (HEPS), escape

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.

- FPVTPQVPLR was recognized in 1 of the 6 women (ML1203), and the response was present in the last available sample prior to seroconversion, 7 months.
- 20/20 sequences of the infecting strain had no substitutions in this epitope, all were FPVTPQVPLR, so there was no evidence for escape.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized in 1/22 HEPS sex worker controls, ML851.

**HXB2 Location** Nef (68–77)

**Author Location** Nef (66–75)

**Epitope** FPVTPQVPLR

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** Nef (68–77)

**Author Location** Nef (68–77 SF2)

**Epitope** FPVTPQVPLR

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3.

**HXB2 Location** Nef (68–77)

**Author Location** Nef (68–77)

**Epitope** FPVTPQVPLR

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B7)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.

- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.

- Subject ML 1203 started with CTL responses to A\*6802 DTVLEDINL and to B7 FPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A\*6802 ETAYFILKL which became dominant, B7 TPGPG(V/I)RYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.

**HXB2 Location** Nef (68–77)

**Author Location** Nef (68–77)

**Epitope** FPVTPQVPLR

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2–8 out of 11 B7-restricted epitopes.
- An acute seroconverter homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

**HXB2 Location** Nef (68–77)

**Author Location** Nef (68–76)

**Epitope** FPVTPQVPLR

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.

- 0/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. Also, none of 4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Nef (68–77)

**Author Location** Nef (66–75)

**Epitope** FPVTPQVPLR

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

**HXB2 Location** Nef (68–77)

**Author Location**

**Epitope** FPVTPQVPLR

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN  
*HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A\*2501, A\*3002; B\*0702, B\*1801

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Nef (68–81)

**Author Location** Nef (82–95 HXB2)

**Epitope** FPVTPQVPLRMTY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Guimarães *et al.* 2002

- Nef sequences were obtained from Brazilians to study epitope diversity in this geographic region—the HXB2 sequence is FPVTPQVPLRMTY, but fpvRpqvplrmty was observed in most Brazilian sequences regardless of the subtype (A, C, D and F).

**HXB2 Location** Nef (68–82)

**Author Location** Nef (68–82)

**Epitope** FPVRPQVPLRPMTYK

**Epitope name** QK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, FPVRPQVPLRPMTYK, is a variant of the consensus peptide QVPLRPMTYKAAVDL.

**HXB2 Location** Nef (68–82)

**Author Location** Nef (68–82)

**Epitope** FPVTPQVPLRPMTFK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, FPVtPQVPLRPMTfK, varies at positions 4 and 14 from the consensus sequence QVPLRPMTYKAAVDL.

**HXB2 Location** Nef (68–82)

**Author Location** Nef (68–82)

**Epitope** FPVRPQVPLRPMTYK

**Epitope name** RY11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide, FPVRPQVPLRPMTYK, was found to have identity with consensus peptide PVRPQVPLRPMTYKA from aa positions 69–82.

**HXB2 Location** Nef (68–82)

**Author Location** Nef (73–82)

**Epitope** FPVRPQVPLRPMTYK

**Subtype** A, D

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0201, A\*0301, B\*4501, B\*5802

**Country** Uganda

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, characterizing CD8+ T cells

**References** Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- This sequence contains a known epitope (RPOVPLRPMTYK). The subject recognizing the peptide carries an HLA allele (A0301) of the known restriction, and the peptide is conserved in the autologous sequence.

**HXB2 Location** Nef (68–84)

**Author Location** Nef

**Epitope** FPVRPQVPLRPMTYKGA

**Immunogen**

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Jubier-Maurin *et al.* 1999

- 41 new HIV-1 strains describing envelope subtypes of HIV-1 A–H were genetically characterized in the nef region – 34 subtypes were classified in the same subtype in nef and env and 7 of the 41 strains were recombinants.
- This region was defined as a CTL epitope region that is conserved among HIV-1 M group subtypes.

**HXB2 Location** Nef (69–83)

**Author Location** Nef

**Epitope** PVRPQVPLRPMTYKA

**Epitope name** nef-5156

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, PVRPQVPLRPMTYKA was mutated in the daughter D2 isolate to PVRPQVPLRPMTfKA.

**HXB2 Location** Nef (70–84)

**Author Location** Nef (70–84 HXB2)

**Epitope** VTPQVPLRPMTYKAA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.



- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 34% of the study subjects, and it was the second most frequently recognized peptide.

**HXB2 Location** Nef (71–79)

**Author Location** Nef (71–79 LAI)

**Epitope** TPQVPLRPM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0702 epitope.

**HXB2 Location** Nef (71–79)

**Author Location** Nef (71–79)

**Epitope** RPQVPLRPM

**Epitope name** RM9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702, B\*4201, B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other

**Keywords** supertype, escape, cross-presentation by different HLA, TCR usage, HLA associated polymorphism

**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction.
- For this epitope, RM9, selection pressure was evidenced by studying changing epitope variants associated with HLAs of the B7 supertype.
- Higher level of sequence variation and escape mutations were associated with the B\*8101 and B\*0702 alleles.

- In 3 B-supertype alleles studied, B\*4201, B\*8101 and B\*0702, two variants were most common - one at the first position, kPQVPLRPM and the other at the sixth position, RPQVPvRPM. Several more variants are listed in the paper.

**HXB2 Location** Nef (71–79)

**Author Location** (C consensus)

**Epitope** RPQVPLRPM

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RPQVPLRPM is an optimal epitope for both B\*4201 and B\*4202.

**HXB2 Location** Nef (71–79)

**Author Location**

**Epitope** RPQVPLRPM

**Epitope name** RM9

**Immunogen**

**Species (MHC)** human (B\*4201)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*4201 epitope.

**HXB2 Location** Nef (71–79)

**Author Location** Nef

**Epitope** RPQVPLRPM

**Epitope name** RM9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201)

**Country** South Africa

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization

**Keywords** rate of progression

**References** Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naïve patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B\*4201 RM9 was used to test 34 patients and gave a median ex vivo tetramer frequency of 0.22.

**HXB2 Location** Nef (71–79)

**Author Location** Nef

**Epitope** RPQVPLRPM

**Epitope name** RM9

**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization  
**Keywords** rate of progression  
**References** Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B\*4201 RM9 was used to test 34 patients and gave a median ex vivo tetramer frequency of 0.22.

**HXB2 Location** Nef (71–79)

**Author Location**

**Epitope** RPQVPLRPM

**Epitope name** RM9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201)

**Country** South Africa

**Assay type** proliferation, Tetramer binding, Intracellular cytokine staining

**References** Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

**HXB2 Location** Nef (71–79)

**Author Location** (C consensus)

**Epitope** RPQVPLRPM

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4202)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- RPQVPLRPM is an optimal epitope for both B\*4201 and B\*4202.

**HXB2 Location** Nef (71–79)

**Author Location** Nef

**Epitope** RPQVPLRPM

**Epitope name** RM9

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*8101)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** rate of progression, HLA associated polymorphism

**References** Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than "other" HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by "other", non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also showed lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variant RPQVPvRPM at position 6 was the predominant polymorphism found.

**HXB2 Location** Nef (71–79)

**Author Location**

**Epitope** TPQVPLRPM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B07)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B07), AN additional HLA (B42) was statistically predicted to be associated with this epitope.

**HXB2 Location** Nef (71–79)

**Author Location** Nef (71–79 BRU)

**Epitope** TPQVPLRPM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** binding affinity, epitope processing

**References** Chopin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.

- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPQVPLRPM was recognized in 1/10 (10%) of individuals with HLA B7, and 1/10 (10%) of individuals with HLA B35. It was a moderate affinity HLA binder.

**HXB2 Location** Nef (71–79)

**Author Location**

**Epitope** RPQVPLRPM

**Epitope name** RM9 ?

**Immunogen** HIV-1 infection

**Species (MHC)** human (B42)

**Country** United States, South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** memory cells

**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** Nef (71–79)

**Author Location** Nef (71–79 SF2)

**Epitope** TPQVPLRPM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3.

**HXB2 Location** Nef (71–79)

**Author Location** Nef (71–79)

**Epitope** TPQVPLRPM

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconverter homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

**HXB2 Location** Nef (71–79)

**Author Location** Nef (71–79 BRU)

**Epitope** TPQVPLRPM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** binding affinity, epitope processing

**References** Chopin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPQVPLRPM was recognized in 1/10 (10%) of individuals with HLA B7, and 1/10 (10%) individuals with HLA B35. It was a moderate affinity HLA binder.

**HXB2 Location** Nef (71–79)

**Author Location** Nef (71–79)

**Epitope** TPQVPLRPM

**Epitope name** B7-TM9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI

this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.

- 0/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Nef (71–79)

**Author Location** Nef

**Epitope** TPQVPLRPM

**Epitope name** B7-TM9(Nef)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A32, B14, B7; A24, B27, B7

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient A displayed the greatest response to epitope B14-EL9(gp41), a strong response to B7-TL9(p24), and responses to B7-TM9(Nef) and A32-PW10(RT). Patient C displayed the greatest response to B27-KK10(p24), and in decreasing order also responded to A24-RW8(Nef), B7-IL9(gp41), A24-RL9(gp41), A24-YL8(gp41), and B7-TM9(Nef).

**HXB2 Location** Nef (71–79)

**Author Location** Nef (180–187)

**Epitope** TPQVPLRPM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Nef (71–79)

**Author Location** Nef

**Epitope** TPQVPLRPM

**Epitope name** B7-TM9(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (71–79)

**Author Location** Nef (71–79)

**Epitope** TPQVPLRPM

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (B7 supertype)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** Nef (71–79)

**Author Location** Nef (C consensus)

- Epitope** RPQVPLRPM  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702, B\*4201, B\*8101, B7, B81)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape, cross-presentation by different HLA  
**References** Kiepiela *et al.* 2004
- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
  - People who carried either B07 or B81 tended to carry a variant of this epitope, while people who did not almost always carried the consensus form.
  - B\*4201 may also present this epitope, as the allele is enriched in people who react with the peptide that contains the epitope, and it is known from the database to be also presented by B\*4201.

**HXB2 Location** Nef (71–79)  
**Author Location** Nef (72–)  
**Epitope** RPQVPLRPM  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7, Cw\*0401)  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons  
**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian subclade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope RPQVPLRPM, is predicted to bind HLAs - B7 and Cw\*0401 with binding affinity scores of 30 and 80.

**HXB2 Location** Nef (71–79)  
**Author Location**  
**Epitope** RPQVPLRPM?  
**Epitope name** RM9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B81)  
**Country** United States, South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding  
**Keywords** memory cells  
**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated

impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** Nef (71–81)  
**Author Location** Nef (75–85 SF2)  
**Epitope** RPQVPLRPMTY

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**References** Tomiyama *et al.* 1997
- A CTL clone responsive to this epitope was obtained.
  - 4/7 B35-positive individuals had a strong CTL response to this epitope.
  - An R to T substitution at position 1 abrogates specific lysis, but not binding to B\*3501.
  - An R to H substitution at position 7 did not alter reactivity.

**HXB2 Location** Nef (71–81)  
**Author Location** Nef (75–85)  
**Epitope** RPQVPLRPMTY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*3501)  
**References** Tomiyama *et al.* 2000a

- CD8+ T-cells that bound one of six HIV-specific B\*3501-epitope tetramers did not express CD28 or CD45A.
- A significant increase in CD28-CD45RA- cells and a decrease of CD28+CD45RA+ cells was observed in chronically HIV-1-infected individuals relative to healthy individuals.
- CD28-CD45RA- cells are likely to be effector cells and have high levels of perforin in their cytoplasm.
- The mean percentage of total CD28- CD8+ cells in chronically infected HIV-1-infected patients was 76.6% in comparison to HIV-1-uninfected individuals (40.6%)

**HXB2 Location** Nef (71–81)  
**Author Location** Nef (75–85 SF2)  
**Epitope** RPQVPLRPMTY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**References** Shiga *et al.* 1996

- Binds HLA-B\*3501.

**HXB2 Location** Nef (71–81)  
**Author Location** (SF2)  
**Epitope** RPQVPLRPMTY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Keywords** binding affinity, rate of progression, escape  
**References** Kawana *et al.* 1999

- HLA B35 is associated with rapid disease progression.
- The sequences of 9 previously described HIV-1 B35 CTL epitopes were obtained in 10 HLA B35+ and 19 HLA B35- individuals.
- 3/9 CTL epitopes had substitutions that were more common in B35+ individuals than in B35- individuals – only one of these reduced the binding of the peptide to B35 and was shown to be an escape mutation.

- rpqvplrpmtF was found in 9/10 of the B35+ individuals, none of the B35- individuals—the Y→F substituted peptide had a similar binding affinity with B35 and was recognized by a CTL clone equally with wildtype.

**HXB2 Location** Nef (71–81)

**Author Location** Nef (69–79)

**Epitope** RPQVPLRPMTY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** Nef (71–81)

**Author Location** Nef (71–81 BRU)

**Epitope** TPQVPLRPMTY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** binding affinity, epitope processing

**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPQVPLRPMTY was recognized in 9/12 (75%) of individuals with HLA B7, and 5/10 (50%) of individuals with HLA B35. It was a moderate affinity HLA binder, and the C-term Y readily cleaved *in vitro*.

**HXB2 Location** Nef (71–81)

**Author Location** Nef

**Epitope** RPQVPLRPMTY

**Subtype** A, B, D

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human, macaque (B51)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost

vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].

- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** Nef (71–81)

**Author Location** Nef (71–81 BRU)

**Epitope** TPQVPLRPMTY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** binding affinity, epitope processing

**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPQVPLRPMTY was recognized in 9/12 (75%) of individuals with HLA B7, and 5/10 (50%) of individuals with HLA B35. It was a moderate affinity HLA binder, and the C-term Y readily cleaved *in vitro*.

**HXB2 Location** Nef (71–81)

**Author Location** Nef (71–81)

**Epitope** TPQVPLRPMTY

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (B7 supertype)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

- A response was induced in one patient after immunization with lipopeptides alone (no adjuvant) after the third (W44) boost. A rPQVPLRPMTY variant was also recognized.

**HXB2 Location** Nef (71–85)

**Author Location** Nef (71–85)

**Epitope** KPQVPLRPMTYKAAV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, KPQVPLRPMTYKAAV, is a variant of the consensus peptide QVPLRPMTYKAAVDL.

**HXB2 Location** Nef (72–81)

**Author Location** Nef (72–82)

**Epitope** PQVPLRPMTY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35, B51)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** Th1, characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Three of nine patients responded to this peptide with GzB producing and IFN-gamma producing cells, and one additional with IFN-gamma producing cells.

**HXB2 Location** Nef (72–86)

**Author Location** Nef (72–86)

**Epitope** PQVPLRPMTYKGAFD

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.

- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.

- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Nef (72–91)

**Author Location** Nef (71–90 SF2)

**Epitope** PQVPLRMTYKAAVDLSHFL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Three of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A3, A32, B51, B62; HLA-A11, A24, B8, B53.

**HXB2 Location** Nef (72–91)

**Author Location** Nef (71–90 SF2)

**Epitope** PQVPLRPMTYKAAVDLSHFL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** Nef (72–91)

**Author Location** Nef (SF2)

**Epitope** PQVPLRRMTYKAAVDLSHFL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- Nef peptides PQVPLRRMTYKAAVDLSHFL, KAAVDLSHFLKEKGGLEGLI and EEEVGFVTPQVPLRPMTY were recognized and the first two share KAAVDLSHFL (a Cw8 epitope), the first and last share PQVPLRPMTY.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 NL43)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**References** Koenig *et al.* 1990

- 81 Tyr is critical for binding to A3.1.
- C. Brander notes that this is an A\*0301 epitope in the 1999 database.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 LAI)

**Epitope** QVPLRPMTYK

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Keywords** rate of progression, escape**References** Koenig *et al.* 1995

- Alanine substitutions L76A, R77A, M79A, T80A significantly decreased immunogenicity of peptide.
- Nef CTL clones (4N225) were infused into an HIV-1 infected volunteer to evaluate effects of infusion on viral load/patient health.
- Infusion led to outburst of escape variants which resulted in higher viral load/accelerated disease progression.

**HXB2 Location** Nef (73–82)**Author Location** Nef (73–82)**Epitope** QVPLRPMTYK**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Keywords** immunodominance**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was A3, and responded to QVPLRPMTYK as well as two other A3.1 epitopes.

**HXB2 Location** Nef (73–82)**Author Location** Nef (73–82)**Epitope** QVPLRPMTYK**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Keywords** acute/early infection**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWILGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVVW, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** Nef (73–82)**Author Location** Nef (73–82 LAI)**Epitope** QVPLRPMTYK**Subtype** B**Immunogen****Species (MHC)** human (A\*0301)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0301 epitope.

**HXB2 Location** Nef (73–82)**Author Location** Nef (73–82)**Epitope** QVPLRPMTYK**Subtype** B**Immunogen** in vitro stimulation or selection**Species (MHC)** human (A\*0301)**Keywords** epitope processing, dendritic cells**References** Andrieu *et al.* 2003

- This study demonstrates that lipopeptides carrying epitopes can be taken up by human dendritic cells, processed using different pathways, and recognized by epitope-specific CD8+ T-cells originally derived from HIV+ individuals. The RT ILKEPVHGV peptide was embedded in a longer peptide fragment in the lipopeptide, and was internalized by endocytosis and processed in the cytosol by proteasomal cleavage by following an endosome-to-cytosol pathway for processing and presentation. Administration of epoxomycin, a proteasome inhibitor, completely abrogated epitope presentation to a CD8+ T-cell line, while monensin, an inhibitor of acid-dependent endosomal enzyme activity did not.
- In contrast to the RT epitope, dendritic cell presentation of the Nef epitope QVPLRPMTYK embedded in a longer peptide in a lipopeptide was not inhibited by epoxomycin, but was inhibited by monensin, indicative of endocytotic epitope processing.

**HXB2 Location** Nef (73–82)**Author Location** Nef**Epitope** QVPLRPMTYK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*0301)**Donor MHC** A\*0101, A\*0301, B\*0801, B\*5101**Country** United Kingdom**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** escape**References** Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient. In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.
- Two variants of this epitope, QVPvRPMTYK and QaPLRPMTYK, were found in 1 donor. The QaPLRPMTYK substitution reduced the binding affinity for A\*0301 by 52%.



- HXB2 Location** Nef (73–82)  
**Author Location** Nef (73–82)  
**Epitope** QVPLRPMTYK  
**Epitope name** QVP  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells  
**References** Turnbull *et al.* 2006
- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
  - This epitope, A3-QVP (that has no association with accelerated or delayed progression to AIDS) and its natural variants are less efficiently cross-recognized. Its alanine-substituted variants were inconsistent between individuals showing very efficient or poor cross-reactivity. CTLs responding to this epitope expressed the same predominant TCR V $\beta$  family, but individuals whose CTLs predominantly used TCR V $\beta$  13.6 had poor cross-recognition of alanine substituted variants.

- HXB2 Location** Nef (73–82)  
**Author Location** Nef  
**Epitope** QVPLRPMTYK  
**Subtype** A, B, D  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag  
**Species (MHC)** human, macaque (A\*0301, A11)  
**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance  
**References** Hanke & McMichael 2000; Wee *et al.* 2002
- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
  - Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5

macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

- HXB2 Location** Nef (73–82)  
**Author Location** Nef (73–82)  
**Epitope** QVPLRPMTYK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*11)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, immunodominance, optimal epitope  
**References** Wang *et al.* 2007
- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
  - This putative epitope, QVPLRPMTYK, was detected and confirmed within overlapping peptides EVGFPVRPQVPLRPMTYK and YKAAVDLSHFLKEKGGL. It was the immunodominant HLA-A\*11 restricted epitope in 10 subjects tested.

- HXB2 Location** Nef (73–82)  
**Author Location** (LAI)  
**Epitope** QVPLRPMTYK  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (A\*1101)  
**Keywords** optimal epitope  
**References** Buseyne 1999; Frahm *et al.* 2008

- HXB2 Location** Nef (73–82)  
**Author Location** Nef (73–82)  
**Epitope** QVPLRPMTYK  
**Subtype** B, CRF01\_AE  
**Immunogen**  
**Species (MHC)** (A\*1101)  
**Country** Thailand  
**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance, structure  
**References** Li & Bouvier 2004
- HLA-A\*1101 has been associated with resistance to acquisition of HIV-1 infection in female sex-workers in Thailand. Its crystal structure has been determined in association with two immunodominant A\*1101 HIV-1 CTL epitopes. Its anchor residues are confirmed as P2(Ile/Val) and C-term (Lys). The backbone conformation of the peptides is defined as two bulges separated by a secondary anchor residue (P6 Ser or

Met) that may offer various advantages in the selection and presentation of CTL epitopes by HLA-A\*1101.

**HXB2 Location** Nef (73–82)

**Author Location** Nef

**Epitope** QVPLRPMTYK

**Epitope name** QK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** HAART, ART, responses in children, dendritic cells

**References** Zhang *et al.* 2006

- Immune responses in HIV-1 infected children either undergoing HAART or not were analysed. HIV-specific CTLs were lower in children responding to HAART than in non-responders and HAART-naïve children. CTL frequency was correlated with myeloid DC frequency in treatment-naïve patients, and inversely correlated with duration of virus suppression following treatment.
- 11 of the 22 children had significant responses to SL9.

**HXB2 Location** Nef (73–82)

**Author Location** Nef

**Epitope** QVPLRPMTYK

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (A03)

**Assay type** Tetramer binding

**Keywords** binding affinity

**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, QVPLRPMTYK (MHC Class I restriction, serotype Bw6) complexed with MHC A03 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

**HXB2 Location** Nef (73–82)

**Author Location**

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (A03)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** Nef (73–82)

**Author Location**

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A03, A11)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 2 alleles previously known to be associated (A03, A11) and 4 additional alleles (A02, A33, B44, Cw07).
- In addition to its known HLA associations (A03, A11), an additional HLA (A34) was statistically predicted to be associated with this epitope.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Le Borgne *et al.* 2000

- Soluble factors in supernatant from both an HIV-specific cloned CTL line and an EBV (Epstein-Barr-virus) CTL line inhibit viral replication, but do not block viral entry in CD4+ T lymphocytes, by a noncytotoxic mechanism.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 LAI)

**Epitope** QVPLRPMTYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Robertson *et al.* 1993

- Development of a retroviral vector (pNeoNef) to generate autologous CTL targets.
- Hunziker *et al.* [1998] suggests that HLA-A2 does not in fact present this epitope.

- The initial assignment of HLA-A2 presentation for this epitope was based on a serological HLA typing. Subsequently, the authors revisited the issue with genetic HLA typing and found that HLA-A11 was the correct presenting molecule (Dr. Florence Buseyne, pers. comm., 2000)

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 LAI)

**Epitope** QVPLRPMTYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** review, escape

**References** Couillin *et al.* 1994; Goulder *et al.* 1997a

- Mutational variation in HIV epitopes in individuals with appropriate HLA types can result in evasion of CTL response.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 LAI)

**Epitope** QVPLRPMTYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Couillin *et al.* 1995

- Mutations found in this epitope in HLA-A11 positive and negative donors were characterized.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Epitope name** QVP

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- One of the 2/8 HLA-A11 study subjects recognized this CTL epitope.
- Patient SC18(HLA A2/11, B8/44, Cw06/0701, DR3/7, DR52/53, DQ2) recognizes the epitopes ACQGVGGPGHK, QVPLRPMTYK, AVDLSHFLK, and one called QIY but not fully described – he had brief therapy upon seroconversion and has had low viral load during 600 days of follow up.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$

**HXB2 Location** Nef (73–82)

**Author Location** Nef (71–80 93TH253 subtype CRF01)

**Epitope** QVPLRPMTYK

**Epitope name** N73-82

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was weakly reactive in HEPS study subjects 265 who was HLA A2/A11 and 128 who was HLA A11/A33, and after a second *in vitro* stimulation, in study subject 256 who was HLA A11/33, making it the most reactive epitope tested in HLA-A11 HEPS women, with 3/4 responding.
- This epitope was strongly reactive in HIV+ study subject 053 who carried HLA-A11.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (71–80 93TH253 subtype CRF01)

**Epitope** QVPLRPMTYK

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined.
- 4/8 tested FSWs recognized this epitope.
- An HLA-A11 tetramer was made for this epitope, which was recognized by two subjects – only one subject had an expanded tetramer staining T-cell population after *in vitro* stimulation.
- This epitope was highly conserved in other subtypes, and exact matches were common.

**HXB2 Location** Nef (73–82)

**Author Location** Nef

**Epitope** QVPLRPMTYK

**Epitope name** QVP

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** Nef (73–82)

**Author Location** Nef

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B60, B8, Bw6

**Keywords** HAART, ART

**References** Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects – two patients recognized this epitope, one using HLA-A3, one using HLA-A11.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Epitope name** QK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** optimal epitope

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Nef (73–82)

**Author Location** Nef

**Epitope** QVPLRPMTYK

**Epitope name** QK9

**Immunogen**

**Species (MHC)** (A11)

**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion

**References** Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** Nef (73–82)

**Author Location** Nef

**Epitope** QVPLRPMTYK

**Epitope name** A11-QK10(Nef)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (73–82)  
**Author Location** Nef (74–82)  
**Epitope** QVPLRPMTYK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11)  
**Donor MHC** A11, A24, B44, B55  
**Country** United Kingdom  
**Assay type** Flow cytometric T-cell cytokine assay, Other  
**Keywords** HAART, ART, immunodominance, TCR usage, memory cells  
**References** Weekes *et al.* 2006

- The effect of HAART on the population size, phenotype and function of HIV- and HCMV-specific CTL clones was analyzed. It was determined that the clonal composition of gag and env HIV-specific CD8 T-cells did not change after HAART. Following HAART, the size of immunodominant HIV-specific CD8 T-cell clones was found to diminish even with the relative preservation of functional memory responses. Maintenance of such strong functional responses implied the preferential loss of HIV-specific cells that have reduced cloning efficiency in vitro. HCMV-specific CTL clones had different kinetics and phenotypes than HIV-specific CTL clones in the same subject.

**HXB2 Location** Nef (73–82)  
**Author Location** Nef (73–82)  
**Epitope** QVPLRPMTYK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301, A11)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B  
**Keywords** Th1, characterizing CD8+ T cells  
**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- None of three patients responded to this peptide with GzB producing cells, while all three responded with IFN-gamma producing cells.

**HXB2 Location** Nef (73–82)  
**Author Location** Nef (73–81)  
**Epitope** QVPLRPMTYK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A11, A2, A3, B35)  
**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** Nef (73–82)  
**Author Location** Nef (73–82 LAI)  
**Epitope** QVPLRPMTYK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Keywords** epitope processing, escape  
**References** Chassin *et al.* 1999

- Mutations in Nef that flank this epitope, Thr71Lys and Ala83Gly, may account for an observed loss of CTL reactivity, with escape due to the introduction of proteasome processing defects.

**HXB2 Location** Nef (73–82)  
**Author Location** Nef (73–82)  
**Epitope** QVPLRPMTYK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Keywords** subtype comparisons  
**References** Durali *et al.* 1998

- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia.
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested.
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag.
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef.
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env.
- One of the patients was shown to react to this epitope: QV-PLRPMTYK.

**HXB2 Location** Nef (73–82)  
**Author Location** Nef (73–82 LAI)  
**Epitope** QVPLRPMTYK  
**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** review, escape

**References** Goulder *et al.* 1997e; Goulder *et al.* 1997a

- HLA-identical siblings, twin hemophiliac brothers, were both infected with the same batch of factor VIII.
- Both had a response to this epitope. One had a response to this epitope, the other did not.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Lubaki *et al.* 1997

- Eighty two HIV-1-specific CTL clones from 5 long-term non-progressors were isolated and analyzed for breadth of response.
- A sustained Gag, Env and Nef response was observed, and clones were restricted by multiple HLA epitopes, indicating a polyclonal response.
- An A3+ subject had a strong response to this epitope, with 10/11 CTL clones being specific for this epitope, isolated at two time points, 1 year apart.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Epitope name** N1

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** HAART, ART, escape

**References** Samri *et al.* 2000

- The epitope was recognized by patients 252#0 and 252#4 in a study of the effects of therapy escape mutations on CTL recognition.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 SF2)

**Epitope** QVPLRRMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.

- Number of HLA-A3+ individuals that had a CTL response to this epitope broken down by group: 3/7 group 1, 1/4 group 2, and 1/2 group 3.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (SF2)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.

**HXB2 Location** Nef (73–82)

**Author Location**

**Epitope** QVPLRPMTYK

**Epitope name** Nef-QK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A03, 9/20 (45%) recognized this epitope.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Epitope name** A3-QK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 3/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 5/7 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Nef (73–82)

**Author Location** Nef

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A3, B44, B64, Bw4, Bw6

**Keywords** HAART, ART

**References** Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects – two patients recognized this epitope, one using HLA-A3, one using HLA-A11.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A1, A3, B14, B7, Cw\*0702, Cw\*0802

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 17 potential epitopes from this individual, defined based on previously identified epitopes presented by appropriate HLA molecules. Full length genome sequence did not reveal changes in time in any of these epitopes over a four year period. Peptide pools initially revealed very little response to these epitopes, but this increased over time.

**HXB2 Location** Nef (73–82)

**Author Location** Nef

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Koning *et al.* 2004

- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
- 3/5 HLA A3+ infection-resistant men, compared to 1/3 pre-seroconversion men who went on to become infected, reacted to this epitope.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (71–80)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong T-helper cell responses. Only patients starting with moderately high viral load (VL) were able to reduce the VL set point. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up.
- 9/14 patients recognized this epitope, it was the most recognized of six A\*03 epitopes.

**HXB2 Location** Nef (73–82)

**Author Location** (B consensus)

**Epitope** QVPLRPMTYK

**Epitope name** QK10

**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A03, B14, B60, Cw3, Cw7; A01, A03, B08, B14, Cw7, Cw8  
**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 2/9 individuals recognized this epitope, presented by HLA-A3.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A2, A3, B44, B7

**Country** United States

**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, escape, variant cross-recognition or cross-neutralization

**References** Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.
- The epitope QVPLRPMTYK was invariant (18/18 sequences) prior to therapy in the patient that recognized it.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A\*0301, A\*7401, B\*1510, B\*3501, Cw\*0401; A\*0301, A\*68, B\*0702, B\*1510, Cw\*0401, Cw\*0702

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection

**References** Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.

- QVPLRPMTYK is the C subtype consensus form of an epitope recognized in a mother, who carried this autologous variant: QVPLRPMTfK. QVPLRPMTfK was the dominant form in her infant at 2 weeks of age, but new variants rapidly emerged: QVPLkPMTfK, QVPLRPMnYK, QVPvRPMTfK, QVPLRPMsYr, QVPLRPMsYK.

**HXB2 Location** Nef (73–82)

**Author Location** Nef

**Epitope** QVPLRPMTYK

**Epitope name** A3-QK10(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRRMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A\*0101, A\*0301, B\*0801

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.



- The best estimates of escape rate for this epitope, QVPLRRM-TYK, were found to be 0.022 and 0.003/day (upper bound on rate of escape = 0.05 and 0.011), with SEs of 0.013 and 0.003 respectively, in 2 subjects.
- In the first subject, a number of mutations arose in Nef 73-82; all but one of these (V74A) elicited a very weak ELISpot response compared to the wild type. In the second subject, large epitope deletions and a V74I substitution in the recognized epitope were selected for.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 LAI)

**Epitope** QVPLRPMTYK

**Epitope name** N1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3 supertype)

**Keywords** HAART, ART, supertype

**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (94–103)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind 3/5 HLA-A3 supertype alleles (A\*0301, A\*1101, A\*3101, A\*3301 and A\*6801).

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 BRU)

**Epitope** QVPLRPMTYK

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11, A3)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 0/9 CRF02\_AG-infected Ivoirians, and 2/9 B-infected French subjects.
- 3/8 Ivoirians carried a substitution in this epitope, while only 1/5 B clade infected French people did, QVPvRPMTYK, and the substitution was found in one of the people that recognized the peptide.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Immunogen** peptide-HLA interaction

**Species (MHC)** (A11, A3, A30)

**Assay type** HLA binding

**Keywords** binding affinity, immunodominance

**References** Racape *et al.* 2006

- Interaction between purified HLA-A3 molecules and several dominant CD8 epitopes was characterized. Amplitude, stability, and kinetic parameters of the interaction between HLA-A3, peptides, and anti-HLA mAbs were tested.
- Epitopes tested bound strongly to HLA-A3 and formed very stable complexes.
- Gag epitope RLRPGGKKK and Nef epitope RLAFFHVAR complexes with HLA-A3 were not recognized by the A11.1 mAb specific to HLA-A3 alleles. The proposed explanation was that Arg at position P1 of the peptide may push the  $\alpha$ 2 helix residue and affect mAb recognition.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 BRU)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11, A3, B35)

**References** Culmann *et al.* 1991

- Nef CTL clones from HIV+ donors.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 LAI)

**Epitope** QVPLRPMTYK

**Subtype** B

**Immunogen**

**Species (MHC)** human (B27)

**References** Culmann 1998

- Optimal epitope mapped by peptide titration.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82 LAI)

**Epitope** SVPLRPMTYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35, Cw4)

**References** Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%.
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM13, who had a CTL response to three epitopes in Nef, was infected via blood transfusion after birth and went from CDC stage P2A to P2E during the study.

**HXB2 Location** Nef (73–82)

**Author Location**

**Epitope** QVPLRPMTYK

**Epitope name** QK10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Country** United States

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** immunodominance, acute/early infection, characterizing CD8+ T cells, immune dysfunction

**References** Lichterfeld *et al.* 2004a

- HIV-1 specific CD8+ T-cells in acute and long-term nonprogressive HIV-1 infection show strong ex-vivo proliferative capacities which are rapidly lost in chronic HIV-1 infection. The loss of CD8+ T-cell function is closely linked with the loss of HIV-1 specific, IL2 secreting CD4+ T-cells. The function can be rescued in vitro and in vivo by restoring the specific CD4+ T-cell help.
- Full CD8+ T-cell responses to this epitope were dependent on co-stimulation with a CD4+ T cell dependent epitope from T-cells harvested during acute infection. The CD8+ T-cell response to this epitope was immunodominant in one study individual.

**HXB2 Location** Nef (73–82)

**Author Location** Nef (73–82)

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Garcia *et al.* 1997

- The anti-Nef CTL line P1 specific for this epitope is able to kill target cells via two mechanisms.
- First: Ca<sup>2+</sup>-dependent, perforin-dependent Nef-specific lysis.
- Second: Ca<sup>2+</sup>-independent, CD95-dependent apoptosis that could also kill non-specific targets.
- Findings indicate that the two mechanisms are not mutually exclusive in human CTL, as they are in mice.
- CTL mediated CD95-dependent apoptosis may play a role in pathogenesis.

**HXB2 Location** Nef (73–82)

**Author Location**

**Epitope** QVPLRPMTYK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, acute/early infection

**References** Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope QVPLRPMTYK seen in 1 patient, underwent sequence changes.

**HXB2 Location** Nef (73–83)

**Author Location** Nef (73–82 BRU)

**Epitope** QVPLRPMTYKA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** binding affinity, epitope processing

**References** Chopin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- QVPLRPMTYKA was recognized in 9/15 (60%) of individuals with HLA A3. It was a high affinity HLA-A3 binder.

**HXB2 Location** Nef (73–88)

**Author Location** Nef

**Epitope** QVPLRPMTYKAAVDL

**Epitope name** nef-5157

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains.

Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.

- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, QVPLRPMTYKAAVDL was mutated in the daughter D2 isolate to QVPLRPMTfKAAVDL.

**HXB2 Location** Nef (73–90)

**Author Location** Nef

**Epitope** QVPLRPMTYKAAVDLSHF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J. Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, QVPLRPMTYKAAVDLSHF, had an overall frequency of recognition of 34% - 40.7% AA, 38.5% C, 29.5% H, 19% WI. This peptide is included in a 58 aa Nef highly reactive region to be used for vaccine design. It is also

part of 'Region I', EVGFPVVRPQVPLRPMTYKAAVDLSHF-FLKEKGGLEGLIYSQK, a 41 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** Nef (74–81)

**Author Location** Nef (74–82)

**Epitope** VPLRPMTY

**Immunogen**

**Species (MHC)** human (A3)

**References** Carreno *et al.* 1992

- Included in HLA-A3 binding peptide competition study.

**HXB2 Location** Nef (74–81)

**Author Location** Nef (74–81)

**Epitope** VPLRPMTY

**Epitope name** VY8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 2 PTE-B peptides, IPLRPMTYK $\gamma$ AIDLS and VPLRPMTY $\gamma$ AArDLS contained the epitope VPLRPMTY (VY8) and elicited IFN-gamma immune responses.

**HXB2 Location** Nef (74–81)

**Author Location** Nef (73–82 LAI)

**Epitope** VPLRPMTY

**Subtype** B

**Immunogen** HIV-1 or HIV-2 infection

**Species (MHC)** human (B\*3501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*3501 epitope.

**HXB2 Location** Nef (74–81)

**Author Location** Nef (75–82)

**Epitope** VPLRPMTY

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B\*3501)

**References** Smith *et al.* 1996

- Crystal structure of VPLRPMTY-class I B allele HLA-B\*3501 complex.

**HXB2 Location** Nef (74–81)

**Author Location** Nef

**Epitope** VPLRPMTY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**Keywords** dendritic cells

**References** Ostrowski *et al.* 2000

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T cell help in 9 of 10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T cell help to a variable degree in most of patients.
- Those CTL that didn't respond to CD40LT could expand with IL2 present, and IL15 produced by dendritic cells also contributes.
- The T-helper epitope used for CD4+ T cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKAN-SKFIGITE)

**HXB2 Location** Nef (74–81)**Author Location** Nef (74–81)**Epitope** VPLRPMTY**Epitope name** VY8**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*3501)**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay**Keywords** escape, acute/early infection**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- Point mutation of epitope at position 8 (Y to F, VPLRPMTf) was detected at a chronic infection timepoint. The CTL response was strong in early infection, but diminished by month 13. This mutation had reduced avidity.

**HXB2 Location** Nef (74–81)**Author Location** Nef**Epitope** VPLRPMTY**Immunogen** HIV-1 infection**Species (MHC)** human (B\*4201, B\*4202)**Country** Kenya**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization**References** Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRF-FKTL (YL9 from Gag protein) was observed and restricted to Cw0304.

- The sequences fpvrpqVPLRPMTYk is associated with HLA-B\*4201/02 and HLA-B\*5301 and contains the epitope VPLRPMTY.

**HXB2 Location** Nef (74–81)**Author Location** Nef (subtype B)**Epitope** VPLRPMTY**Subtype** B**Immunogen** HIV-1 exposed seronegative**Species (MHC)** human (B35)**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNT-VATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** Nef (74–81)**Author Location** Nef**Epitope** VPLRPMTY**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Keywords** acute/early infection**References** Wilson *et al.* 2000a

- Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
- All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B2705; and A\*0201, A\*0301, B2705, B39.
- ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWIIIGGLNK.
- The subject with A\*0201 had a moderately strong response to SLYNTVATL.
- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** Nef (74–81)**Author Location** Nef (73–82 LAI)**Epitope** VPLRPMTY**Subtype** B**Immunogen** HIV-1 or HIV-2 infection**Species (MHC)** human (B35)**Keywords** review

- References** Culmann *et al.* 1991; McMichael & Walker 1994
- Review of HIV CTL epitopes – defined by B35 motif found within a larger peptide.

**HXB2 Location** Nef (74–81)

**Author Location** Nef (75–82 LAI)

**Epitope** VPLRPMTY

**Subtype** B, HIV-2

**Immunogen** HIV-1 or HIV-2 infection

**Species (MHC)** human (B35)

**Country** Gambia

**Keywords** HIV exposed persistently seronegative (HEPS), HIV-2

**References** Rowland-Jones *et al.* 1995

- VPLRPMTY was recognized by CTL from HIV-1-infected and HIV-2-infected B35+ subjects; epitope is conserved between HIV-1 and HIV-2.

**HXB2 Location** Nef (74–81)

**Author Location** Nef

**Epitope** VPLRPMTY

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B35)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A and D subtype consensus are identical to the B clade epitope.

**HXB2 Location** Nef (74–81)

**Author Location** Nef (75–82)

**Epitope** VPLRPMTY

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (B35)

**References** Lalvani *et al.* 1997

- A peptide-based protocol was optimized for restimulation of CTLp using optimized peptide and IL-7 concentrations – importantly this protocol does not stimulate a primary response, only secondary – peptide-specific CTLp counts could be obtained via staining with peptide-Class I tetramers.
- This peptide was one of the B35 presented test peptides used in control experiments showing that the assay gave no activity using lymphocytes from 21 healthy B35 seronegative donors.

**HXB2 Location** Nef (74–81)

**Author Location** Nef (subtype B)

**Epitope** VPLRPMTY

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B35)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.

- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A, B, and D clade viruses.

**HXB2 Location** Nef (74–81)

**Author Location** Nef

**Epitope** VPLRPMTY

**Immunogen**

**Species (MHC)** human (B35)

**References** Rowland-Jones *et al.* 1999

- CTL responses in seronegative highly HIV-exposed African female sex workers in Gambia and Nairobi were studied – these women had no delta 32 deletion in CCR5.
- In Gambia there is exposure to both HIV-1 and HIV-2, CTL responses to B35 epitopes in exposed, uninfected women are cross-reactive,
- HIV-2 version of this epitope is conserved: VPLRPMTY, and CTLs are cross-reactive – one of five B35 CTL epitopes that are cross-reactive, see also Rowland-Jones *et al.* [1995]

**HXB2 Location** Nef (74–81)

**Author Location** Nef (74–81)

**Epitope** VPLRPMTY

**Epitope name** VPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** HAART, ART, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- One of two HLA B35+ among the eight study subjects recognized this epitope.
- Patient SC15 (HLA A1/68, B8/35, Bw4/6, Cw4/0704) was given acute and sustained therapy and recognized epitopes PPIPVGDIY and VPLRPMTY during 331 days of HAART treatment.

**HXB2 Location** Nef (74–81)

**Author Location** Nef (75–82)

**Epitope** VPLRPMTY

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B35)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Subject ML 857 shifted from a A\*6802 DTVLEDINL and B35 (H/N)PDIVYQY response prior to seroconversion to a B35 PPIPVGDIY and B35 VPLRPMTY response post-seroconversion.

**HXB2 Location** Nef (74–81)**Author Location****Epitope** VPLRPMTY**Epitope name** Nef-VY8**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B35, 12/22 (55%) recognized this epitope.
- Among HIV+ individuals who carried HLA B\*5301, 0/11 (0%) recognized this epitope.

**HXB2 Location** Nef (74–81)**Author Location** Nef (74–81 BRU)**Epitope** VPLRPMTY**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Keywords** binding affinity, epitope processing**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- VPLRPMTY was recognized in 5/16 (31%) of individuals with HLA B35, and it was a moderate affinity HLA binder. Cleavage at the C-term Y was frequent *in vitro*.

**HXB2 Location** Nef (74–81)**Author Location****Epitope** VPLRPMTY**Subtype** A, B, D**Immunogen** HIV-1 infection, vaccine*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade HIV component: p17 Gag, p24 Gag**Species (MHC)** human, macaque (B35)**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** Nef (74–81)**Author Location** Nef (74–81)**Epitope** VPLRPMTY**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Donor MHC** A1, A3, B35, B8**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** acute/early infection, early treatment**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. SubjectBroadcast message from root Thu May 27 21:34:36 2004...n of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma vBattery Low Notification from APM BIOS (8% 0:12) or the frequency of IFN $\gamma$  secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** Nef (74–81)**Author Location** Nef (72–79)**Epitope** VPLRPMTY**Immunogen** HIV-1 infection

- Species (MHC)** human (B35)  
**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004
- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
  - Less than 2 of 9 patients recognized this epitope.
- HXB2 Location** Nef (74–81)  
**Author Location** Nef (C consensus)  
**Epitope** VPLRPMTY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** escape  
**References** Kiepiela *et al.* 2004
- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
  - People who carried B35 carried a variant of this epitope, while people who did not almost always carried the consensus form.
- HXB2 Location** Nef (74–81)  
**Author Location** Nef (72–79)  
**Epitope** VPLRPMTY  
**Epitope name** VPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, escape  
**References** Oxenius *et al.* 2004b
- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes were recognized 0–80% as efficiently as the index peptide, and the relatively efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.
- VPL epitope was one of six that were largely or completely replaced by escape variants, with the two escape forms coming up between days 172 and 635, vplrpmSy and vplrmpTF.
- HXB2 Location** Nef (74–81)  
**Author Location** Nef  
**Epitope** VPLRPMTY  
**Epitope name** B35-VY8(Nef)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006
- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
  - The most frequently recognised epitopes also elicited the greatest CTL response.
  - HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
  - HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
  - In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.
- HXB2 Location** Nef (74–82)  
**Author Location** Nef (73–82)  
**Epitope** VPLRPMTYK  
**Immunogen** peptide-HLA interaction  
**Species (MHC)** human (A11)  
**References** Zhang *et al.* 1993
- Exploration of A11 binding motif.
- HXB2 Location** Nef (74–88)  
**Author Location** Nef (74–88)  
**Epitope** IPLRPMTYKGALDLS  
**Epitope name** FL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7 supertype)  
**Donor MHC** B\*1503, B35, B7 supertype, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** computational epitope prediction, vaccine-induced epitopes  
**References** Li *et al.* 2006b
- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that

vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.

- This epitope, IPLRPMTYK<sub>g</sub>AIDLS, varies from the consensus peptide at positions 10 and 12.

**HXB2 Location** Nef (75–82)

**Author Location** Nef (75–82 LAI)

**Epitope** PLRPMTYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** review

**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.
- C. Brander notes that this is an A\*1101 epitope in the 1999 database.

**HXB2 Location** Nef (75–82)

**Author Location** Nef (75–82 LAI)

**Epitope** PLRPMTYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*1101 epitope.

**HXB2 Location** Nef (76–85)

**Author Location** Nef (77–)

**Epitope** LRPMTKGAF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*2702, B\*2705)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope LRPMTKGAF, is predicted to bind HLAs - B\*2702 and B\*2705 with binding affinity scores of 200 and 1000.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (77–85)

**Epitope** RPMTYKGAL

**Epitope name** RL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07-super)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.

- 2 PTE-B peptide sequences were identified, IPLRPMTYK<sub>g</sub>AIDLS and VPLRPMTYrAArDLS, containing variants of this consensus epitope sequence RL9, viz. RPMTYK<sub>g</sub>AL and RPMTYrAAr, both of which elicited IFN-gamma immune responses.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (77–85 LAI)

**Epitope** RPMTYKAAL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**Keywords** escape

**References** Bauer *et al.* 1997

- Structural constraints on the Nef protein may prevent escape.
- Noted in Brander 1999, this database, to be B\*0702.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (77–85 LAI)

**Epitope** RPMTYKAAL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0702 epitope.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (75–83 IIIB)

**Epitope** RPMTYKAAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** binding affinity, TCR usage

**References** Oxenius *et al.* 2001b

- Study of tetramer staining of B7 around RPMTYKAAL gave quantitative results that were very different than functional measurements based on an ELISPOT assay.
- Autologous clones were checked and 39/40 clones from two time points had the variant sequence RPMTYKGAL – tetramers based on RPMTYKGAL gave a more intense and uniform staining and bound with higher affinity to the RPM-TYKGAL V $\beta$ 14 TCR.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (77–85 SF2)

**Epitope** RPMTYKAAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b



- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 1/4 group 1, 0/3 group 2, and 1/1 group 3.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (77–85)

**Epitope** RPMTYKAAAL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconverter homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (77–85)

**Epitope** RPMTYKAAAV

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
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- The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (77–85 BRU)

**Epitope** RPMTYKAAV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** binding affinity, epitope processing

**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- RPMTYKAAV was recognized in 7/10 (70%) of individuals with HLA B7, and 0/3 (0%) of individuals with HLA B35. It was a moderate affinity HLA binder.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (77–85)

**Epitope** RPMTYKAAAL

**Epitope name** B7-RL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 3/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (77–85)

**Epitope** RPMTYKAAV

**Epitope name** B7-RV9

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Donor MHC** A3, B7, Cw7**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 2/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 3/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Nef (77–85)**Author Location** Nef (75–83)**Epitope** RPMTYKAAL**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Country** Spain**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/7 patients recognized this epitope.

**HXB2 Location** Nef (77–85)**Author Location** Nef (75–83)**Epitope** RPMTYKGAL**Epitope name** RPM**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Donor MHC** A2, A68.1, B\*07, B\*3503, Cw\*0401, Cw\*0702, DQ2, DQ6, DR15, DR17, DR51, DR52**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, escape**References** Oxenius *et al.* 2004b

- The increase in plasma viral load in a patient that progressed rapidly was preceded by positive selection of viral escape mutations in epitopes targeted by dominant HIV-1-specific CD8+ T-cell responses, and a decrease in HIV-1-specific CD4+ and CD8+ T-cell frequencies. Overall, escape variant epitopes

were recognized 0-80% as efficiently as the index peptide, and the relative efficiency of the variant epitopes increased using PBLs collected after their appearance. No changes were found in viral tropism, replication kinetics and neutralizing antibody titers, so the rapid decline of the patient was attributed to loss of HIV containment due to CTL escape.

- This epitope was one of six epitopes found to be under positive selection for escape mutations and was completely replaced by escape variants between days 172 and 635 (rpmtFkgal, rpm-SykAal, rpmtkygaV, rpmtkyAal). The first two were the most common at day 635, and experimentally shown to be escape.

**HXB2 Location** Nef (77–85)**Author Location** Nef**Epitope** RPMTYKGAL**Epitope name** RL9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Donor MHC** A1, A3, B57, B7, Cw6, Cw7**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 4, RPMnYKGAL, was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** Nef (77–85)**Author Location** Nef (77–85 BRU)**Epitope** RPMTYKAAV**Subtype** B, CRF02\_AG**Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Country** Cote D'Ivoire**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02\_AG-infected Ivorians, and 2/9 B-infected French subjects.
- One of the B-clade infected subjects that recognized this peptide was not sequenced, the other had one amino acid change: RPMTYKAAI. A variant form was in 3/5 B clade infection sequences. 8/8 CRF01 infected individuals had a variant of this peptide.

**HXB2 Location** Nef (77–85)**Author Location** Nef (77–85)

- Epitope** RPMTYKAAL  
**Epitope name** RW9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Donor MHC** A\*24, A\*30, B\*07, B\*39, Cw\*12, Cw\*17  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Sanchez-Merino *et al.* 2005
- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
  - Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
  - The variant RPTMThqAAW was present in 10/10 clones from a B7- mother, was transmitted to her B7+ infant, and present in 29/30 clones at months 2, 6, and 152.

**HXB2 Location** Nef (77–85)

**Author Location** Nef (79–85)

**Epitope** RPMTYKAAV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A3, A33, B14, B35, Cw\*0401, Cw\*0802

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, early treatment

**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** Nef (77–91)

**Author Location** Nef

- Epitope** RPMTYKAAVDLSHFL  
**Epitope name** nef-5158  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)  
**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism  
**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, RPMTYKAAVDLSHFL was mutated in the daughter D2 isolate to RPMTfKAAVDLSHFL.

**HXB2 Location** Nef (77–91)

**Author Location** Nef (77–91)

**Epitope** RPMTYKAALDLSHFL

**Epitope name** AL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Donor MHC** A23, B62

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.

- This peptide, RPMTYKAAIDLSHFL, varies at position 9 from the consensus peptide RPMTYKAAVDLSHFL.

**HXB2 Location** Nef (77–91)  
**Author Location** Nef (77–91)  
**Epitope** RPMTYKGAVDLSHFL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B62)  
**Donor MHC** A23, B62  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** computational epitope prediction, vaccine-induced epitopes  
**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, RPMTYK<sub>g</sub>AVDLSHFL varies at position 7 (glycine) from the consensus peptide YKAAVDLSHFLKEKG.

**HXB2 Location** Nef (77–91)  
**Author Location** Nef (77–91)  
**Epitope** RPMTYKGAFDLSFFL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons  
**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Nef (78–87)  
**Author Location** Nef (79–)  
**Epitope** PMTKGAFDL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons  
**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope PMTKGAFDL, is predicted to bind HLA-A2 with a binding affinity score of 105.79.

**HXB2 Location** Nef (78–92)  
**Author Location** Nef (78–92)  
**Epitope** PMTYKAAVDLSHFLK  
**Epitope name** AK9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A24, A3, B7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** computational epitope prediction, vaccine-induced epitopes  
**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope, PMTYKAAVDLSHFLK, has identity with the consensus peptide YKAAVDLSHFLKEKG from positions 81-92.

**HXB2 Location** Nef (78–92)  
**Author Location** Nef (78–92)  
**Epitope** PMTYKAAVDLSHFLK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B62)  
**Donor MHC** A23, B62  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** computational epitope prediction, vaccine-induced epitopes  
**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.

- This peptide, PMTYKAAVDLSHFLK has identity with the consensus peptide YKAAVDLSHFLKEKG from positions 81-92.

- HXB2 Location** Nef (78–92)  
**Author Location** Nef (78–92)  
**Epitope** PMTYKGAFDLSHFLK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B62)  
**Donor MHC** A23, B62  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** computational epitope prediction, vaccine-induced epitopes  
**References** Li *et al.* 2006b
- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
  - This peptide, PMTYK<sub>g</sub>AfDLSHFLK, varies at positions 6 and 8 from the consensus peptide YKAAVDLSHFLKEKG.

- HXB2 Location** Nef (79–87)  
**Author Location** Nef (81–89 HXB3)  
**Epitope** MTYKAALDL  
**Immunogen** vaccine  
*Vector/Type:* DNA, peptide *Strain:* B clade HXB3 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (A\*0201)  
**Keywords** binding affinity, computational epitope prediction  
**References** Sandberg *et al.* 2000
- Ten Nef 9-mer peptides were predicted to have a strong binding affinity with HLA-A\*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly.
  - A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with either nef DNA under the control of a CMV promoter coated on, gold particles delivered to abdominal skin by gene gun.
  - MTYKAALDL bound weakly to HLA-A2, but the DNA nef vaccine elicited a good CTL response.

- HXB2 Location** Nef (79–87)  
**Author Location** Nef (79–87)  
**Epitope** MTYKAALDL  
**Epitope name** Nef79-87  
**Immunogen** HIV-1 infection  
**Species (MHC)** human, humanized mouse (A2)  
**Country** United States

- Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** responses in children, immunodominance, characterizing CD8+ T cells

- References** Chandwani *et al.* 2004
- Responses to five HLA-A2 presented epitopes in Nef were characterized in a population of 19 HIV infected adults and 21 children. The CD8 T-cell response to Nef was stronger and broader in adults than children, averaging 652 and 87 SFCs/10<sup>6</sup> PBMC, and 2.6 and 0.9 recognized epitopes per person, respectively.
  - This is one of three novel Nef epitopes previously identified in HLA-A2 transgenic mice, shown to induce CD8 T-cell response in humans. It was not the immunodominant response.

- HXB2 Location** Nef (79–87)  
**Author Location** Nef  
**Epitope** MTYKAAVDL  
**Subtype** B, C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B63)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, cross-presentation by different HLA  
**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. There is no evidence for B57/B58 cross-presentation of this epitope.

- HXB2 Location** Nef (79–87)  
**Author Location** Nef (81–)  
**Epitope** MTYKGALDL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons  
**References** Kumar *et al.* 2006a
- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
  - Of the most common HLA in India tested, this epitope, MTYKGALDL, is predicted to bind 50% of them with high affinity.

- HXB2 Location** Nef (79–87)  
**Author Location** Nef (77–)  
**Epitope** MTYKGAVDL  
**Subtype** A

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons  
**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope, MTYKGAVDL, is predicted to associate with 50% of them.

**HXB2 Location** Nef (79–93)  
**Author Location** Nef  
**Epitope** MTYKGAFDLSHFLKE  
**Subtype** A, D  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*6601, A\*6801, B\*5301, B\*5802; A\*0202, A\*3002, B\*5703, B\*5802  
**Country** Uganda  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, characterizing CD8+ T cells  
**References** Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- Novel unmapped epitope, this test peptide was conserved in the people that recognized it.

**HXB2 Location** Nef (80–87)  
**Author Location** Nef (80–87)  
**Epitope** TYKAAVDL  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21  
**Species (MHC)** human (A24)  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization  
**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** Nef (80–87)  
**Author Location** Nef (80–87 BRU)  
**Epitope** TYKAAVDL  
**Subtype** B, CRF02\_AG  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A24)  
**Country** Cote D'Ivoire  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons  
**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 1/9 CRF02\_AG-infected Ivoirians, and 0/9 B-infected French subjects.
- This epitope was highly variable in Ivoirians; 8/9 had amino acid substitutions. The only one that reacted carried the sequence TYKgAfDL. 3/5 of the B clade French subjects carried variants, which tended to have only 1 amino acid substitution.

**HXB2 Location** Nef (80–94)  
**Author Location** Nef (80–94 HXB2)  
**Epitope** TYKAAVDLSHFLKEK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** T-cell Elispot  
**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment  
**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 47% of the study subjects, and it was the most frequently recognized peptide.

**HXB2 Location** Nef (81–97)  
**Author Location** Nef  
**Epitope** YKGALDLSHFLKEKGG  
**Epitope name** NEF-12  
**Subtype** B

**Immunogen** HIV-1 infection**Species (MHC)** human**Country** China**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, immunodominance**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, yKGAIDLShFLKEKGGGL differs from the consensus C sequence fKGAfDLSfFLKEKGGGL at 3 amino acid positions, i.e. by 17.6%.

**HXB2 Location** Nef (81–97)**Author Location** Nef**Epitope** YKAAVDLSHFLKEKGGGL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Country** Barbados, Haiti, United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other**Keywords** binding affinity, immunodominance**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved

peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, YKAAVDLSHFLKEKGGGL, had an overall frequency of recognition of 30% - 33.9% AA, 30.8% C, 31.8% H, 14.3% WI. This peptide is included in a 58 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region I', EVGFVPRPQVPLRPMTYKAAVDLSHFLKEKGGGLEGLIYSQK, a 41 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** Nef (82–90)**Author Location** (C consensus)**Epitope** KGAFDLSFF**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*57)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** characterizing CD8+ T cells**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Nef (82–90)**Author Location** Nef (82–90)**Epitope** KAAVDLSHF**Epitope name** KF9**Subtype** B, C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*57, B\*5801)**Country** Australia**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding**Keywords** subtype comparisons, computational epitope prediction, mother-to-infant transmission, escape, viral fitness and reversion, optimal epitope**References** Leslie *et al.* 2005

- KAAVDLSHF is the susceptible optimal form of the epitope, and KgAVDLSHF an escape variant. The KgAVDLSHF form of the epitope was shown to be an escape mutation by virtue of an increased off-rate; however Elispot reactions to both forms are positive. The escape form was shown to be transmitted, and the most common form of the epitope in a B clade infected population in Perth, Australia (52%).

**HXB2 Location** Nef (82–90)

**Author Location** Nef

**Epitope** KAAFDLSFF

**Epitope name** KF9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57, B\*5801)

**Country** Australia

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, HLA associated polymorphism

**References** Bhattacharya *et al.* 2007

- Host HLA associated mutational patterns in HIV can be a consequence of immune escape, but to cleanly resolve whether or not such patterns are the result of lineage effects or immune pressure, it is helpful to incorporate the phylogenetic history of the virus into the test statistics. Most of the HLA associations that appeared to result from immune escape in an earlier study (Moore *et al.*, *Science* 296:1439 2002) were found to be a consequence of the phylogenetic history of the virus, not immune escape. Other HLA associations were validated, and some additional HLA-associated mutations were identified through incorporating the viral phylogenetic tree in the analysis.
- There are two variant forms of this B57/B5801 epitope at the second position KaAFDLSFF and KgAFDLSFF. Leslie *et al.*, *J Exp Med.* 2005 201:891 suggest that the escape form KgAFDLSFF may have come to dominate the C clade lineage over time due to higher HLA B57/B5801 frequencies in southern Africa. Bhattacharya suggests lineage effects are also playing an important role in the observed amino acid frequencies, and note that the ratio of G/A has not change over time, and that the frequency of G/A in different epidemic populations does not correlate with HLA B57/B5801 allele frequency.

**HXB2 Location** Nef (82–90)

**Author Location** Nef (C consensus)

**Epitope** KAAFDLSFF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, viral fitness and reversion

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- People who carried B57 all carried a variant of this epitope, while about half of the people who did not carry B57 carried the susceptible form, suggesting there is not a high fitness cost and reversion rate in this case.
- HLA-B57 was associated with a low viral load.

**HXB2 Location** Nef (82–90)

**Author Location** Nef (82–90)

**Epitope** KAAFDLSFF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A\*3001, A\*66, B\*4201, B\*5802, Cw\*0602, Cw\*1701; A\*66, A\*68, B\*57, B\*5802, Cw\*0602, Cw\*0701

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection

**References** Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- KAAFDLSFF is the C consensus form of the epitope; the autologous form in the mother was KAAFDLgFF, and this was transmitted to her infant. By 33 weeks a new dominant form of the epitope had emerged in the infant: gAAFDLgFF.

**HXB2 Location** Nef (82–90)

**Author Location**

**Epitope** KAAVDLSHF

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** Nef (82–91)

**Author Location** Nef (82–91)

**Epitope** KAALDLSHFL

**Subtype** B

**Immunogen** vaccine



*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A2)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that the vaccinated volunteers responded to.
- A KAAVDLSHFL variant was cross-recognized after the last boost.

**HXB2 Location** Nef (82–91)

**Author Location** Nef (82–91 LAI)

**Epitope** KAAVDLSHFL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0802)

**Keywords** HAART, ART

**References** Nixon *et al.* 1999

- A patient who made a mono-specific CTL response to this Nef specific epitope was given effective anti-retroviral therapy within 90 days of infection, reducing the antigenic stimulus.
- Within 7 days of therapy, his CTLp frequency dropped from 60 to 4 per million PBMC, as his viremia dropped.
- The patient went from having an activated effector population (detected by CTLp and clone specific RNA) to a non-activated quiescent population (detected by the CTL-clone specific DNA)

**HXB2 Location** Nef (82–91)

**Author Location**

**Epitope** KAAVDLSHFL

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw08)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KAAVDLSHFL elicited a magnitude of response of 540 SFC with a functional avidity of 0.01nM.

**HXB2 Location** Nef (82–91)

**Author Location**

**Epitope** KAAVDLSHFL

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw08)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (Cw08), an additional HLA (Cw03) was statistically predicted to be associated with this epitope.

**HXB2 Location** Nef (82–91)

**Author Location** Nef (82–91 SF2)

**Epitope** KAAVDLSHFL

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-Cw8+ individuals that had a CTL response to this epitope broken down by group: 1/3 group 1, 0/0 group 2, and 0/1 group 3.

**HXB2 Location** Nef (82–91)

**Author Location** Nef (SF2)

**Epitope** KAAVDLSHFL

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw8)

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.

**HXB2 Location** Nef (82–91)

**Author Location** (B consensus)

**Epitope** KAAVDLSHFL

**Epitope name** KL10

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (Cw8)**Donor MHC** A25, A32, B08, B14, Cw7, Cw8**Country** United States**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells**References** Lichtenfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
- 1/9 individuals recognized this epitope.

**HXB2 Location** Nef (82–91)**Author Location** Nef**Epitope** KAAVDLSHFL**Epitope name** KL10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (Cw8)**Donor MHC** A28, A29, B14, B44, Cw8**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 6, KAAVDmSHFL, was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** Nef (82–91)**Author Location****Epitope** KAAVDLSHFL**Epitope name** KL10**Immunogen****Species (MHC)** human (Cw8)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is a Cw08 epitope.

**HXB2 Location** Nef (82–96)**Author Location** Nef (82–96)**Epitope** KGAFDLSFFLKEKGG**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Nef (82–101)**Author Location** Nef (81–100 SF2)**Epitope** KAAVDLSHFLKEKGGLEGLI**Immunogen** HIV-1 infection**Species (MHC)** human**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Three of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A1, A2, B8, B14; HLA-A11, A24, B8, B53.

**HXB2 Location** Nef (82–101)**Author Location** Nef (SF2)**Epitope** KAAVDLSHFLKEKGGLEGLI**Immunogen** HIV-1 infection**Species (MHC)** human**References** Altfeld *et al.* 2001a

- HIV+ individual AC-06 was tested for reactive overlapping peptides spanning all HIV-1 proteins in an ELISPOT and was found to react with 12 peptides from 7 proteins, suggesting that the breadth of CTL responses are underestimated if accessory proteins are not included in the study.
- Nef peptides PQVPLRRMTYKAAVDLSHFL, KAAVDLSHFLKEKGGLEGLI and EEEVGFVPTQPVPLRPMY were recognized and the first two share KAAVDLSHFL (a Cw8 epitope), the first and last share PQVPLRPMY.

**HXB2 Location** Nef (83–90)**Author Location** Nef (83–90 HXB2)**Epitope** AAVDLSHF**Subtype** B, CRF01\_AE**Immunogen** HIV-1 infection**Species (MHC)** human (B62)**Country** Viet Nam**Assay type** HLA binding**Keywords** subtype comparisons, computational epitope prediction, escape, variant cross-recognition or cross-neutralization, vaccine antigen design**References** Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in

- epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01\_AE variant GaFDlsFf had a higher HLA-B62 binding score than the HXB2 epitope.

**HXB2 Location** Nef (83–91)  
**Author Location** Nef (83–91)  
**Epitope** AAVDLSHFL  
**Epitope name** AL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*02)  
**Country** United States  
**Assay type** Intracellular cytokine staining, Other  
**Keywords** rate of progression, escape, immune evasion  
**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- The AL9 epitope AAVDLSHFL elicited a potent CTL response while its minor variant AAVDiSHFL containing substitution L87I at position 5 elicited a less intense response, resulting in the L87I variant later dominating the viral population. This is a novel viral adaptation to an HLA-A2 restricted immune response discovered in Nef epitope AL9. In later longitudinal studies, more variants were seen either linked - AAVDirHFL - or not linked with the L87I mutant. Two new mutants seen were the A83G at position 1, gAIDLSHFL and gArDLSHFL; and the V85L at position 3, AAIDLSHFL, AAIDiSHFL, AAIDiSHIL. Amino acid positions 83, 85, 97 and 91 were under positive selection pressure.
- Responses to AL9 were seen in early chronic infection.

**HXB2 Location** Nef (83–91)  
**Author Location** Nef (85–93 HXB3)  
**Epitope** AALDLSHFL  
**Immunogen** vaccine  
*Vector/Type:* DNA, peptide *Strain:* B clade HXB3 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (A\*0201)  
**Keywords** binding affinity, computational epitope prediction  
**References** Sandberg *et al.* 2000

- Ten Nef 9-mer peptides were predicted to have strong binding affinity for HLA-A\*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly.
- A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with nef DNA under the control of a CMV promoter, coated on gold particles delivered to abdominal skin by gene gun.
- AALDLSHFL was predicted to have a strong binding capacity for HLA-A2, and did, but it was the only one of the peptides recognized that was a strong binder, the other two recognized peptides were weak binders.
- AALDLSHFL was also tested by subcutaneous injection of Nef peptides in Freund's adjuvant and gave a strong response to the peptide.

**HXB2 Location** Nef (83–91)  
**Author Location** (C consensus)  
**Epitope** GAFDLSFFL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0205)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- GAFDLSFFL is an optimal epitope.

**HXB2 Location** Nef (83–91)  
**Author Location** Nef (83–91)  
**Epitope** GAFDLSFFL  
**Epitope name** GL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0205)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008  

- C. Brander notes this is a A\*0205 epitope.

**HXB2 Location** Nef (83–91)  
**Author Location** Nef  
**Epitope** GAFDLSFFL  
**Epitope name** GL9  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0205)  
**Country** South Africa  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization  
**Keywords** rate of progression  
**References** Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naive patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer A\*0205 GL9 was used to test 11 patients and gave a median ex vivo tetramer frequency of 0.48.

**HXB2 Location** Nef (83–91)

**Author Location**

**Epitope** GAFDLSFFL?

**Epitope name** GL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205)

**Country** United States, South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** memory cells

**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91)

**Epitope** GAFDLSFFL

**Epitope name** GL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0205)

**Country** South Africa

**Assay type** proliferation, Tetramer binding, Intracellular cytokine staining

**References** Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91 BRU)

**Epitope** AAVDLSHFL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** binding affinity, epitope processing

**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.

- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- AAVDLSHFL was recognized in 3/18 (17%) of individuals with HLA A2. It was a low affinity HLA binder.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91)

**Epitope** AAVDLSHFL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A2)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that the vaccinated volunteers responded to.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91)

**Epitope** AALDLSHFL

**Epitope name** Nef83-91

**Immunogen** HIV-1 infection

**Species (MHC)** human, humanized mouse (A2)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, immunodominance, characterizing CD8+ T cells

**References** Chandwani *et al.* 2004

- Responses to five HLA-A2 presented epitopes in Nef were characterized in a population of 19 HIV infected adults and 21 children. The CD8 T-cell response to Nef was stronger and broader in adults than children, averaging 652 and 87 SFCs/10<sup>6</sup> PBMC, and 2.6 and 0.9 recognized epitopes per person, respectively.
- The novel AALDLSHFL Nef epitope was the most frequently and most strongly recognized epitope in this study, making it a possible immunodominant epitope.
- This is one of three novel Nef epitopes previously identified in HLA-A2 transgenic mice, shown to induce CD8 T-cell response in humans.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91 BRU)

**Epitope** AAVDLSHFL

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

- Country** Cote D'Ivoire  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons  
**References** Inwoley *et al.* 2005
- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivorian subjects.
  - This epitope was recognized by 1/9 CRF02\_AG-infected patients, and by 1/9 B-infected patients. Variants were present in 6/8 Ivorians, and in 3/5 French subjects.
  - The Ivorian who recognized the B clade peptide carried the substitutions gAfDLSHFL.
- HXB2 Location** Nef (83–91)  
**Author Location** Nef (83–91 HXB2)  
**Epitope** AAVDLSHFL  
**Subtype** B, CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** Viet Nam  
**Assay type** HLA binding  
**Keywords** subtype comparisons, computational epitope prediction, escape, variant cross-recognition or cross-neutralization, vaccine antigen design  
**References** Lazaro *et al.* 2005
- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
  - The CRF01\_AE variant GaFdsFfl had a higher HLA-A2 binding score than the HXB2 epitope.
- HXB2 Location** Nef (83–91)  
**Author Location** Nef (83–91)  
**Epitope** AAVDLSHFL  
**Epitope name** AL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Donor MHC** A\*02, A\*30, B\*13, B\*18, Cw\*01, Cw\*05; A\*02, A\*32, B\*07, B\*40, Cw\*03, Cw\*07  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Sanchez-Merino *et al.* 2005
- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.

- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- An escape form of the A2 epitope, AAVDmSHFL, was transmitted from an A2- mother to her A2+ infant, where it persisted in 29/29 sequences sampled over 11 months.
- Another form of this A2 epitope, gAIDLSHFL, was transmitted by an A2+ mother to an A2- infant, where it persisted in 30/30 sequences sampled over 15 months.
- AAVDmSHFL was shown to have lower responder cell frequencies than AAVDLSHFL.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–)

**Epitope** GAFDLSFFL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*0205, A2, B7, B8, Cw\*0602)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian subclade. Potential epitopes were computationally predicted within these Nef proteins.
- This epitope GAFDLSFFL, is predicted to bind 80% of HLA molecules screened including HLAs - A2, A\*0201, A\*0205, B7, B8 and Cw\*0602 with predicted binding affinity scores of 14.947, 143.58, 7.56, 12, 1.2 and 6.6 respectively.

**HXB2 Location** Nef (83–91)

**Author Location** Nef

**Epitope** AAVDLSHFL

**Epitope name** A68-AL(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A68)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91)

**Epitope** AAVDLSHFL

**Epitope name** AL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*62, Cw\*08)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 5 additional variants of this epitope, AAVDLSHFL, were seen - gAVDLSHFL, AAiDLSHFL, AAIDLSHFL, gAIDLSHFL and gAfDLSHFL. The last 3 variants show lower avidity than responses to the consensus epitope do.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91)

**Epitope** AAVDLSHFL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60, B62, Cw\*0802, Cw8)

**Donor MHC** A\*0201, A23, B44, B62, Cw3, Cw4; A1, A3, B14, B7, Cw\*0702, Cw\*0802; A\*0201, A31, B44, B60, Cw16, Cw3; A1A1, B14, B8, Cw7, Cw8

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, early treatment

**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- Four different individuals recognized this epitope during a primary infection, and it was shown to be presented by HLA B60, B62, C2\*0802, and Cw8.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91)

**Epitope** AAVDLSHFL

**Epitope name** AL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (C\*03)

**Assay type** CTL suppression of replication

**Keywords** class I down-regulation by Nef

**References** Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Nef epitope AAVDLSHFL-recognizing HLA-C restricted CTLs were unaffected by Nef.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91 LAI)

**Epitope** AAVDLSHFL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0802)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a C\*0802(Cw8) epitope. Variant gAfDLSfFL also noted.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91)

**Epitope** AALDLSHFL

**Immunogen**

**Species (MHC)** human (Cw3)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Nef (83–91)

**Author Location** Nef (83–91)

**Epitope** AALDMSHFL

**Epitope name** AL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw3)

**Donor MHC** A\*0201, A\*2402, B\*4001, B\*5001, Cw03, Cw04

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells

**References** Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third

brother, infected by the twins' virus 13 months after their sero-conversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.

- This epitope, AALDMSHFL (AL9), is restricted by HLA-Cw3. Variants that arose were AALDiSHFL and gALDMSHFL.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (81–)

**Epitope** GAVDLSHFL

**Subtype** A

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope, GAVDLSHFL, is predicted to associate with 50% of them.

**HXB2 Location** Nef (83–91)

**Author Location** Nef (139–)

**Epitope** GALDLSHFL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope, GALDLSHFL, is predicted to bind 40% of them with high affinity.

**HXB2 Location** Nef (83–91)

**Author Location**

**Epitope** AAVDLSHFL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0101; B\*0801, B\*1401

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.

- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- AAVDLSHFL was recognized by a placebo patient after infection.

**HXB2 Location** Nef (83–92)

**Author Location** Nef (83–92)

**Epitope** AAVDLSHFLK

**Epitope name** AK10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*11)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 2 PTE-B peptide sequences were identified, PMTYKAAVDLSHFLK and GAIDLSHFLKEKGGGL, containing variants of this consensus epitope sequence AK10, viz. AAVDLSHFLK and GAIDLSHFLK, both of which elicited IFN-gamma immune responses.

**HXB2 Location** Nef (83–92)

**Author Location** Nef (81–90 93TH253 subtype CRF01)

**Epitope** GAFDLSFFLK

**Epitope name** N83-92

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Sriwanthana *et al.* 2001

- This was a study of HIV-1 exposed persistently seronegative (HEPS) female sex workers in Chiang Mai, northern Thailand.
- HLA-A11 is very common in this population, and was enriched among the HEPS sexworkers – weak CTL responses were detected in 4/7 HEPS women, and CTL responses were found in 8/8 HIV+ controls, and 0/9 HIV- women that were not exposed.
- This epitope was strongly reactive in HIV+ study subjects 053 and 184 who carried HLA-A11.

**HXB2 Location** Nef (83–92)

**Author Location** Nef (81–90 93TH253 subtype CRF01)

**Epitope** GAFDLSFFLK

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- HLA-A11 CRF01 (called subtype E in Bond *et al.*) epitopes were identified that stimulated CTL from HIV+ female sex workers (FSW) from Northern Thailand, of whom more than half were HLA-A11 positive.
- 77 possible HLA-A11 epitopes were first defined using EpiMatrix, these were screened for binding to A11 finding and 26 bound, and 12 of these were epitopes for CTL responses from 8 HLA-A11 positive FSWs, six were novel, six were previously identified.
- This epitope was predicted by the EpiMatrix method to be likely to bind to A11, and it served as an epitope in the FSWs, it was one of the six A11 epitopes that had been previously defined.
- 4/8 tested FSWs recognized this epitope.
- This epitope was only conserved in CRF01 and subtype C, and exact matches were uncommon.

**HXB2 Location** Nef (83–92)

**Author Location** Nef (83–92)

**Epitope** AAVDLSHFLK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A\*0201, A11, B51, B61, Cw\*14, Cw2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, early treatment

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15–92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN- $\gamma$  secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.

**HXB2 Location** Nef (83–94)

**Author Location** Nef (83–94 BRU)

**Epitope** AAVDLSHFLKEK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Culmann *et al.* 1991

- Epitope defined by boundaries of overlapping peptides that stimulate Nef CTL clones.

**HXB2 Location** Nef (83–97)

**Author Location** Nef (83–97)

**Epitope** GALDLSHFLKEKGGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide GAIDLSHFLKEKGGL varies at position 3 (leucine) from the consensus peptide YKAAVDLSHFLKEKGGL.

**HXB2 Location** Nef (84–91)

**Author Location** Nef (84–91)

**Epitope** ALDLSHFL

**Epitope name** AL8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- A PTE-B peptide, GAIDLSHFLKEKGGL contained the epitope ALDLSHFL (AL8) and elicited an IFN- $\gamma$  immune response.

**HXB2 Location** Nef (84–91)

**Author Location** Nef (84–91)

**Epitope** AVDLSHFL

**Subtype** B

**Immunogen** vaccine



*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A2)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that the vaccinated volunteers responded to.

**HXB2 Location** Nef (84–91)

**Author Location** Nef (84–91 LAI)

**Epitope** AVDLSHFL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**References** Culmann-Penciolelli *et al.* 1994

**HXB2 Location** Nef (84–91)

**Author Location** Nef (84–91)

**Epitope** AVDLSHFL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for IFN $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope.

**HXB2 Location** Nef (84–91)

**Author Location** Nef (84–91 BRU)

**Epitope** AVDLSHFL

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 2/9 CRF02\_AG-infected Ivoirians, and 0/9 B-infected French subjects.

- The 2 CRF02 infected subjects that recognized this peptide carried a form with one amino acid change: AfDLSHFL. Variant forms were in 4/8 CRF02 infection sequences. 3/5 B clade infected individuals had a variant of this peptide.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92)

**Epitope** AVDLSHFLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92)

**Epitope** AVDLSHFLK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*11)

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** assay standardization/improvement, optimal epitope

**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This putative epitope, AVDLSHFLK, was detected and confirmed within overlapping peptides SHFLKEKG-GLEGLIYSQK and YKAAVDLSHFLKEKGGL.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92 LAI)

**Epitope** AVDLSHFLK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*1101 epitope.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92)

**Epitope** AVDLSHFLK

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*1101)

**Keywords** subtype comparisons

**References** Fukada *et al.* 2002

- Counterparts for eight known clade B HLA A\*1101 epitopes were generated for clade E (CRF01). Three epitopes, identical among clade A-E, were cross-reactive and recognized by clade E infected individuals. The clade E and B analogs to three more HLA A\*1101 epitopes was recognized in a clade specific manner. Two other HLA A\*1101 clade B defined epitopes were found not to have stimulated a response in clade E infected individuals.
- AVDLSHFLK was found to elicit clade-specific responses in clade B (AVDLSHFLK is most common, aLdlshflk is a common variant also found in clade A) and clade E (aFdlsFflk is most common and is also common in clade C). AVDLSHFLK was strongly recognized by CTL from 2/5 B clade infected Japanese subjects, as was aLdlshflk, and aFdlsFflk by CTL from 5/7 E clade infected Thai subjects.
- The binding of aFdlsFflk to HLA A\*1101 was 10-50 times lower than the other variants, and bulk CTL generated from individuals did not cross-react with the cross-clade peptides.

**HXB2 Location** Nef (84–92)

**Author Location** Nef

**Epitope** AVDLSHFLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A03, A11)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope AVDLSHFLK when restricted by HLA-A03 elicited a magnitude of response of 620 SFC with a functional avidity of 0.5nM and binding affinity of 0.65nM. When restricted by HLA-A11, it elicited a magnitude of response of 50 SFC with a functional avidity of 0.5nM and binding affinity of 5.9nM.

**HXB2 Location** Nef (84–92)

**Author Location**

**Epitope** AVDLSHFLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A03, A11)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the

presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.

- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 2 alleles previously known to be associated (A03 and A11) and 4 additional alleles (A02, A23, A30, B44).

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–)

**Epitope** AFDLSFFLK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope AFDLSFFLK, is predicted to bind HLA-A1 with a binding affinity score of 2.5.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92 LAI)

**Epitope** AVDLSHFLK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** review

**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.
- C. Brander notes that this is an A\*1101 epitope in the 1999 database.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92)

**Epitope** AVDLSHFLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals that didn't respond to SLYNTVATL reacted with seven other epitopes including this epitope.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92 LAI)

**Epitope** AVDLSHFLK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** review, escape

**References** Couillin *et al.* 1994; Goulder *et al.* 1997a

- Mutational variation in HIV epitopes in individuals with appropriate HLA types can result in evasion of CTL response.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92 LAI)

**Epitope** AVDLSHFLK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Couillin *et al.* 1995

- Mutations found in this epitope in HLA-A11 positive and negative donors were characterized.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92)

**Epitope** AVDLSHFLK

**Epitope name** AVD

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- Both of the 2/8 HLA-A11 study subjects recognized this CTL epitope.
- Patient SC19(HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSHFLK, and FNCGGEFFY that declined during therapy initiated at day 197.
- Patient SC18(HLA A2/11, B8/44, Cw06/0701, DR3/7, DR52/53, DQ2) recognizes the epitopes ACQGVGGPGHK, QVPLRPMTYK, AVDLSHFLK, and one called QIY but not fully described – he had brief therapy upon seroconversion and has had low viral load during 600 days of follow up.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (82–90)

**Epitope** AVDLSHFLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92 SF2)

**Epitope** AVDLSHFLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HAART, ART, acute/early infection

**References** Altfield *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A11+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/0 group 2, and 2/2 group 3.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92)

**Epitope** AVDLSHFLK

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (A11)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** Nef (84–92)

**Author Location** Nef

**Epitope** AVDLSHFLK

**Epitope name** AVD

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** Nef (84–92)

**Author Location** Nef

**Epitope** AVDLSHFLK

**Subtype** A, B, D, F

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human, macaque (A11)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92)

**Epitope** AVDLSHFLK

**Epitope name** AK9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** optimal epitope

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92)

**Epitope** AVDLSHFLK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Nef (84–92)

**Author Location** Nef

**Epitope** AVDLSHFLK

**Epitope name** A11-AK9(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (B consensus)

**Epitope** AVDLSHFLK

**Epitope name** AK9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11, A3)

**Donor MHC** A02, A11, B18, B44, Cw12, Cw5; A03, B14, B60, Cw3, Cw7

**Country** United States

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, cross-presentation by different HLA, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.

- 2/9 individuals recognized this epitope, each in the context of a different HLA-presenting molecule.

**HXB2 Location** Nef (84–92)  
**Author Location** Nef (84–92 BRU)  
**Epitope** AVDLSHFLK  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Keywords** binding affinity, epitope processing  
**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- AVDLSHFLK was recognized in 4/12 (33%) of individuals with HLA A3. It was a high affinity HLA-A3 binder.

**HXB2 Location** Nef (84–92)  
**Author Location** Nef (84–94)  
**Epitope** AVDLSHFLK  
**Epitope name** A3-ALK9  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A3, B7, Cw7  
**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection  
**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/14 HLA-A3 positive individuals had detectable A3-restricted responses to this epitope during acute infection, but only 5/15 of HLA-A3 epitopes tested were targeted during acute infection. 1/7 individuals began to have detectable responses to this epitope after STI.

**HXB2 Location** Nef (84–92)  
**Author Location** Nef (84–92)  
**Epitope** AVDLSHFLK  
**Epitope name** AK9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)  
**Donor MHC** A\*03, A\*31, B\*08, B\*15, Cw\*04, Cw\*07; A\*24, A\*31, B\*15, B\*47, Cw\*04, Cw\*07  
**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- Variant sequence aMdlshflk was present in 7/10 clones from A3+ mother, was transmitted and present in 10/10 clones at months 2 and 4, but dropped to 0/10 clones by 15 months of age in her A3- child.

**HXB2 Location** Nef (84–92)  
**Author Location** Nef

**Epitope** AVDLSHFLK  
**Epitope name** A3-AK9(Nef)  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A3)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognized epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (84–92)  
**Author Location** Nef (84–92)

**Epitope** AVDLSHFLK  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A11, A3)  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization  
**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+ T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** Nef (84–92)

**Author Location** Nef (84–92 BRU)

**Epitope** AVDLSHFLK

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11, A3)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivorian subjects.
- This epitope was recognized by 0/9 CRF02\_AG-infected Ivorians, and 2/9 B-infected French subjects.
- One of the B-clade infected subjects that recognized this peptide carried the identical form, the other had one amino acid change: AIDLSHFLK. This variant form was in 3/5 B clade infection sequences. 4/8 CRF01 infected individuals had a variant of this peptide.

**HXB2 Location** Nef (84–92)

**Author Location**

**Epitope** AVDLSHFLK

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A\*0201, A\*1101; B\*4002, B\*5101

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85–86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it both before and after infection.

**HXB2 Location** Nef (85–99)

**Author Location** Nef

**Epitope** VDLSHFLKEKGGLEG

**Epitope name** nef-5160

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, VDLSHFLKEKGGLEG was mutated in the daughter D2 isolate to VDLSHFLKEmGGLdG.

**HXB2 Location** Nef (86–94)

**Author Location** Nef (84–92 LAI)

**Epitope** DLSHFLKEK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0301)

**Keywords** review

**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.

**HXB2 Location** Nef (86–94)

**Author Location** Nef

**Epitope** DLSHFLKEK

**Subtype** A, B, D, F

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade *HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human, macaque (A\*0301)

**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

- HXB2 Location** Nef (86–94)  
**Author Location** Nef (86–94)  
**Epitope** DLSHFLKEK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0301, A11)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B  
**Keywords** Th1, characterizing CD8+ T cells  
**References** Kleen *et al.* 2004
- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
  - Two of nine patients responded to this peptide with GzB producing cells, while three of the patients responded with IFN-gamma producing cells. Only one patient had both GzB and IFN-gamma responses.
- HXB2 Location** Nef (86–94)  
**Author Location** Nef (86–94)  
**Epitope** DLSHFLKEK  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (A3)  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2001a
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

- HXB2 Location** Nef (86–94)  
**Author Location** Nef (86–94 HXB2)  
**Epitope** DLSHFLKEK  
**Subtype** B, CRF01\_AE  
**Immunogen** HIV-1 infection

- Species (MHC)** human (A11, A3)  
**Country** Viet Nam  
**Assay type** HLA binding  
**Keywords** subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design  
**References** Lazaro *et al.* 2005
- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
  - The CRF01\_AE variant dlsFflkek had same HLA-binding score as the HXB2 epitope.

- HXB2 Location** Nef (86–100)  
**Author Location** Nef (86–100 LAI)  
**Epitope** DLSHFLKEKGGLEGL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**References** Robertson *et al.* 1993
- Development of a retroviral vector (pNeoNef) to generate autologous targets.

- HXB2 Location** Nef (86–100)  
**Author Location** Nef (86–100 LAI)  
**Epitope** DLSHFLKEKGGLEGL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**References** Buseyne *et al.* 1993b

- HXB2 Location** Nef (86–100)  
**Author Location** Nef (86–100 LAI)  
**Epitope** DLSHFLKEKGGLEGL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35, Cw4)  
**References** Buseyne *et al.* 1993a
- Vertical transmission of HIV ranges from 13% to 39%
  - Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
  - Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
  - Patient EM13, who had a CTL response to three epitopes in Nef, was infected via blood transfusion after birth and went from CDC stage P2A to P2E during the study.

- HXB2 Location** Nef (87–102)  
**Author Location** Nef  
**Epitope** FSHFLKEKGGLEGLIY  
**Immunogen**  
**Species (MHC)** human  
**Keywords** subtype comparisons  
**References** Jubier-Maurin *et al.* 1999

- 41 new HIV-1 strains describing envelope subtypes of HIV-1 A-H were genetically characterized in the nef region – 34 subtypes were classified in the same subtype in nef and env and 7 of the 41 strains were recombinants.
- This region was defined as a CTL epitope region that is conserved among HIV-1 M group subtypes.

**HXB2 Location** Nef (88–100)

**Author Location** Nef (103–116)

**Epitope** SHFLKEKGGLEGL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Guimarães *et al.* 2002

- Nef sequences were obtained from Brazilians to study epitope diversity in this geographic region—most B subtype sequences are SHFLKEKGGLEGL, but sFLkekgglegl is found in most subtype C samples.

**HXB2 Location** Nef (88–105)

**Author Location** Nef

**Epitope** SHFLKEKGGLEGLIYSQK

**Epitope name** NEF-13

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, ShFLKEKGGLEGLIYSqK differs from the consensus C sequence SfFLKEKGGLEGLIYSkK at 2 amino acid positions, i.e. by 11.1%.

**HXB2 Location** Nef (88–105)

**Author Location** Nef

**Epitope** SHFLKEKGGLEGLIYSQK

### Subtype B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, SHFLKEKGGLEGLIYSQK, had an overall frequency of recognition of 18% - 20.3% AA, 30.8% C, 15.9% H, 0% WI. This peptide is included in a 58 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region I', EVGFPVVRPQVPLRPMTYKAAVDLSHFLKEKGGLEGLIYSQK, a 41 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** Nef (89–97)

**Author Location** Nef (89–)

**Epitope** FFLKEKGG

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0401)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.



- Of the most common HLA in India tested, this epitope FFLKEKGGGL, is predicted to bind HLA-Cw\*0401 with a binding affinity score of 200.

**HXB2 Location** Nef (89–103)

**Author Location** Nef

**Epitope** HFLKEKGGLEGLIYS

**Epitope name** nef-5161

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, HFLKEKGGLEGLIYS was mutated in the daughter D2 isolate to HFLKEmGGLdGLIYS.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (90–97)

**Epitope** FLKEKGGGL

**Epitope name** BRU

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2, B8)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 1/9 CRF02\_AG-infected Ivoirians, and 2/9 B-infected French subjects.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Keywords** dendritic cells

**References** Ostrowski *et al.* 2000

- The role of CD4+ T-cell help in expansion of virus-specific memory CTL was studied through co-culture *ex vivo*
- Optimal expansion of HIV-1-specific memory CTL depended on CD4+ T cell help in 9 of 10 patients – CD40 ligand trimer (CD40LT) could enhance CTL in the absence of CD4+ T cell help to a variable degree in most of patients.
- Those CTL that didn't respond to CD40LT could expand with IL2 present, and IL15 produced by dendritic cells also contributes.
- The T-helper epitope used for CD4+ T cell stimulation was the universal tetanus helper epitope TET830-843 (QYIKAN-SKFIGITE)

**HXB2 Location** Nef (90–97)

**Author Location**

**Epitope** FLKEKGGGL

**Epitope name** Nef-FL8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*08)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B\*08, 1/3 (33%) recognized this epitope.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (SF2)

**Epitope** FLKEKGGGL

**Epitope name** FL8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*08)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining

**Keywords** TCR usage

**References** Meyer-Olson *et al.* 2006

**HXB2 Location** Nef (90–97)

**Author Location**

**Epitope** FLKEKGGGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*08)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** characterizing CD8+ T cells

**References** Addo *et al.* 2007

- Maturation phenotypes of CTLs were compared between HIV-1 Controller and Progressor subjects. Controllers were found to recognize a median of 18 epitopes compared to 15 by Progressors. While Controllers certainly had higher frequencies of terminally differentiated effector CTLs (CD45RA+/CCR7-), Progressors had higher

mean frequencies of CD45RA-/CCR7- effector memory, CD45RA-/CCR7+ central memory (statistically significant) and CD45RA+/CCR7+ naive CTLs. No correlation was seen between CTL effector phenotype and either HLA-type or epitope.

- B\*08-restricted epitope FLKEKGGL does not correlate with any particular CTL maturation phenotype.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (89–96)

**Epitope** FLKEKGGL

**Epitope name** FL8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*08)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** rate of progression, acute/early infection, memory cells

**References** Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope FL8, FLKEKGGL, IFN-gamma and TNF-alpha were produced by CD127 lo cells in chronic patients with viremia. IL-2 was produced by both CD127 hi and lo cells.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (89–97 LAI)

**Epitope** FLKEKGGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0801 epitope.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (90–97)

**Epitope** FLKEKGGL

**Epitope name** FL8

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Donor MHC** A\*0201, A\*2402, B\*0801, B\*5701, Cw\*0602, Cw\*0701; A\*0101, A\*0201, B\*0801, B\*5701, Cw\*0602, Cw\*0701; A\*2402, A2, B\*0801, B15, Cw12, Cw7; A\*0101, A\*0201, B\*0801, B\*5701, Cw\*0602, Cw\*0701

**Country** United Kingdom

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape, TCR usage, characterizing CD8+ T cells

**References** Dong *et al.* 2004

- In 4 donors with delayed disease progression, the response to the FL8 Nef epitope was dominated by V-beta-13.2 TCR expressing CTLs with an unusually long CDR3 region. These CTLs were shown to be resistant to apoptosis and able to recognize escape variants of the FL8 Nef epitope. Thus, selection of these CTLs may be related to better clinical outcome.

- The Q5 variant flkeQggl was rapidly selected in a donor that responded to the FLKEKGGL epitope. The FLKEKGGL peptide and the variant flkeQggl HLA-B8 complexes bound to the Vbeta13.2 FLKEKGGL TCR with equal affinity, while the Vbeta6 FLKEKGGL TCR had reduced affinity for the FLKEKGGL form and did not recognize the Q5 variant. Other variants (T5, N5, and M5 as well as Q5) were recognized by Vbeta13.2 clones from all 4 donors. One clone from donor 046 that was not Vbeta13.2 could only recognize the index variant.

**HXB2 Location** Nef (90–97)

**Author Location** (C consensus)

**Epitope** FLKEKGGL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Donor MHC** A\*0101, B\*0801

**Country** United Kingdom

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** escape, acute/early infection

**References** Milicic *et al.* 2005

- CTL responses and escape were analyzed in 4 homosexual couples where blood samples were available within weeks of estimated transmission. When the recipient had the same HLA type as the donor, CTL escape variants prevented a CTL response to those epitopes in the recipient. Even when the HLA alleles were different in the transmitting couple, a single escape mutation in one epitope can abolish CTL recognition of an overlapping epitope of distinct restriction in the recipient.

In an early acute infection of the donor, the precise timing of transmission determines the viral variants transmitted.

- The recipient mounted an acute CTL response to this epitope, and the escape variant flkeQggl emerged soon after.

**HXB2 Location** Nef (90–97)

**Author Location** (C consensus)

**Epitope** FLKEKGGL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- FLKEKGGL is an optimal epitope.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGL

**Epitope name** FL8

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Country** South Africa

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Degranulation, CD107a and b cell surface mobilization

**Keywords** rate of progression

**References** Day *et al.* 2007

- Eight epitopes and 113 subjects were used to test whether correlations existed between HIV-1 Clade C viral load and CTL proliferation, cytokine production or degranulation in therapy-naïve patients. Only CTL proliferation showed a strong inverse correlation with viral load.
- The tetramer B\*0801 FL8 was used to test 26 patients and gave a median ex vivo tetramer frequency of 0.40.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGL

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (B\*0801)

**Assay type** Tetramer binding

**Keywords** binding affinity

**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently

expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.

- This epitope, FLKEKGGL (MHC Class I restriction, serotype Bw6) complexed with MHC B\*0801 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (90–97)

**Epitope** FLKEKGGL

**Epitope name** FLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells

**References** Turnbull *et al.* 2006

- Functional cross-reactivity of CD8 responses to HIV-1 epitopes restricted by different HLA-alleles was analyzed. It was shown that epitope-specific responses with the most efficient cross-recognition were strongly associated with delayed disease progression. Variant-cross recognition efficiency was linked to the dominant TCRs used for epitope recognition. Epitopes restricted by the same HLA-allele did not show similar variant cross-recognition efficiency, suggesting that the rate of disease progression might be associated with the quality of responses to certain critical epitopes.
- This epitope, B8-FLK that is associated with more rapid progression to AIDS and its natural as well as alanine-substituted variants were quite weakly cross-recognized. CTLs responding to this epitope expressed the same predominant TCR Vbeta family.

**HXB2 Location** Nef (90–97)

**Author Location**

**Epitope** FLKEKGGL

**Epitope name** FL8

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0801)

**Country** South Africa

**Assay type** proliferation, Tetramer binding, Intracellular cytokine staining

**References** Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (89–97 LAI)

**Epitope** FLKEKGGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** review, escape

**References** Price *et al.* 1997

- CTL escape variants appeared over time in HLA-B8 HIV-1 + individual, providing evidence of immune escape.

- Most variants appear at position 5, an anchor residue.
- FLKE(E,N or Q)GGL showed reduced binding efficiency and recognition.
- Double mutants (FIKENGGL, FLEENGGL, and FLKGNGGL) completely escaped recognition.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study in the context of CTL escape to fixation.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (90–97 IIIB)

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART, responses in children

**References** Spiegel *et al.* 1999

- Study examines the effect of highly active antiretroviral therapy (HAART) on HIV-1 plasma viral load, CTLp and CTLc frequencies in 8 infected children.
- CTLp (precursors) were measured by stimulating in culture and assaying using 51Cr release, against vaccinia expressed IIIB Env, Gag, Pol, Nef.
- B7-FLKEKGGL tetramer complex was used for one of the children that was HLA-B7, and this infant showed a vigorous response (> 4% of CD8+ T cells) at 9 months of age.
- HIV-1 specific CTL responses initially increased in children with complete viral suppression, but then decreased, suggesting viral replication is needed to maintain CTL responses.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGL

**Immunogen** vaccine

*Vector/Type:* vaccinia

**Species (MHC)** human (B8)

**References** Hanke *et al.* 1998a; Hanke *et al.* 1998b

- This epitope was shown to be processed and presented to appropriate CTL clones upon infection of human target cells with vaccinia virus Ankara (VVA) carrying 20 HIV-1 epitopes recognized by humans.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (88–95)

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Goulder *et al.* 1997g

- Natural variants for this epitope have been observed in several donors.
- Substitutions Q5, N5, E5 that alter anchor position 5 are not well recognized.
- Substitution I2 binds well to B8 and is recognized.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (90–97)

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Dyer *et al.* 1999

- CTL specific responses were measured over a 1.3 to 1.5 year period in members of the Sydney Blood Bank Cohort (SBBC) who had been infected with a natural attenuated strain of HIV-1 which was Nef-defective.
- Some of these patients had prolonged high levels of CTL effector and memory cells despite low viral load.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (SF2)

**Epitope** FLKEKGGL

**Epitope name** FL8

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Goulder *et al.* 2001a

- This peptide elicited a weak CTL response during acute HIV-1 infection in patient PI004.
- Three CTL responses, to epitopes TSTLQEQIGW, ISPRTLNAW, and KAFSPEVIPMF, were evident early after infection; CTL responses to SLYNTVATL, QASQEVKNW, EIYKRWII, and FLKEKGGL were detectable at 5 months post-infection and beyond.
- FL8 was recognized in an additional patient, AC29, in chronic infection.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (92–99)

**Epitope** FLKEKGGL

**Epitope name** FLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART

**References** Oxenius *et al.* 2001a

- Characterization of specific CTL phenotype patterns in response to variation of the virus load in response to antiviral therapy in 3 patients with chronic HIV-1 infection.
- CTL activation in response to increasing viral load sequential, and co-segregated with apoptosis only during later stages of the response, suggesting antigen-specific cell-death is restricted to distinct CTL sub-populations.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (92–99)

**Epitope** FLKEKGGL

**Epitope name** FLK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART, supervised treatment interruptions (STI), immunodominance, escape, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- Six of the 7/8 study subjects that were HLA B8 recognized this early dominant CTL epitope.

- Patient SC2 (HLA A1, B7/8, Cw0701/0702, DR4/53, DQ7) had CTL responsiveness against epitopes FLKEKGGL, GP-KVKQWPL, and GEIYKRWII peptides – FLKEKGGL tetramer staining steadily declined and at day 1340 the FLKEKGGL stained cells were no longer detected and the escape mutant FLKENGGI was found in 8/10 clones.
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDWYHTQGYFPDWQNY, and GEIYKRWII peptides and all responses declined during therapy initiated at day 390 but were restored when therapy became intermittent.
- Patient SC19 (HLA A11/12, B8/44, Cw06/0701, DR3/7, DR52/53, DQ 2/8) had a CTL response to epitopes FLKEKGGL, GEIYKRWII, ACQGVGGPGHK, AVDLSH-FLK, and FNCGGEFFY that declined during therapy initiated at day 197.
- Patient SC10 (HLA A1/3, B8/35, DR1/8, DQ 4/5) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL and a response to GEIYKRWII through day 1088.
- Patient SC12 (HLA A1, B8/39, Cw0701/0702, DR2/3, DR51/52, DQ2/6) had sustained therapy started during acute infection and maintained an immunodominant response to FLKEKGGL throughout and minor responses to GEIYKRWII, DCKTILKAL, GGKKKYKLLK – GEIYKRWII and GGKKKYKLLK responses were stimulated by a brief period off therapy.
- Patient SC11 (HLA A1, B8, Cw0201, DR3/11, DR52, DQ2/7) started therapy early, remained on therapy for 40 days, then reinitiated HAART at day 640 had a CTL response to FLKEKGGL, GPKVKQWPL, and GEIYKRWII throughout and received a benefit from the early limited course therapy.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Kostense *et al.* 2001

- HLA tetramers to six epitopes were used to study HLA-A2, B8 and B57 CTL in 54 patients – HIV-specific tetramer positive cells were inversely correlated with viral load in patients with high CD4, but in patients with CD4 T-cells below 400 high tetramer frequencies were found despite high viral load.
- Most patients have high levels of HIV-specific T-cell expansions, but many of these cells aren't functional.
- In 15 of the patients, the proportion of IFN gamma producing tetramer cells correlated with AIDS-free survival.
- Stimulation with HLA-B8 p24 and Nef epitopes significantly increased Nef-specific T-cell numbers in 2 patients (748 and 1113)
- There were more functional IFN-gamma producing Nef-specific T-cells within the T-cell population than there were active p24 Gag-specific T-cells.
- No correlation between elevated numbers of Nef-specific CTL cells and plasma viral load was observed.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (88–95)

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (88–95 SF2)

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Keywords** HAART, ART, acute/early infection

**References** Altfield *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B8+ individuals that had a CTL response to this epitope broken down by group: 3/3 group 1, 1/3 group 2, and 1/2 group 3.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (89–97)

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$

**HXB2 Location** Nef (90–97)

**Author Location** Nef (90–97)

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**References** Day *et al.* 2001

- B8-restricted CTL accounted for about 1/3 of the total CTL response in one individual.
- The response to FLKEKGGL was the second highest response in magnitude compared to all the HLA class I A- and B-restricted epitopes tested in this individual.

**HXB2 Location** Nef (90–97)**Author Location** Nef**Epitope** FLKEKGGL**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**References** Goulder *et al.* 2000b

- Tetramer assays were compared with three functional assays in 42 people with chronic HIV infection: ELISPOT, intracellular cytokine staining, and precursor frequency (limiting dilution assay [LDA])
- HIV-specific tetramer staining CTLs appeared to be active, and inert CTL were not found to play a significant role in chronic pediatric or adult HIV infection.

**HXB2 Location** Nef (90–97)**Author Location** Nef (90–97 BRU)**Epitope** FLKEKGGL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Keywords** binding affinity, epitope processing**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- FLKEKGGL was recognized in 12/14 (86%) of individuals with HLA B8, and it was a high affinity HLA binder.

**HXB2 Location** Nef (90–97)**Author Location** Nef**Epitope** FLKEKGGL**Epitope name** FLK**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Keywords** HAART, ART, supervised treatment interruptions (STI)**References** Oxenius *et al.* 2002b

- Using previously defined epitopes Oxenius *et al.* [2000, 2001a] in an IFN $\gamma$  Elispot assay, 13 chronically HIV-1 infected patients were studied over a period including therapy with standard treatment interruptions (STI).
- STIs induced increased recognition of CTL epitopes, but there was no correlation between CTL responses with viral rebound rates, plateau viral loads, or clearance rates.

**HXB2 Location** Nef (90–97)**Author Location** Nef**Epitope** FLKEKGGL**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Donor MHC** A11, A2, B60, B8, Bw6**Keywords** HAART, ART**References** Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects – two patients recognized FLKEKGGL.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

**HXB2 Location** Nef (90–97)**Author Location** Nef**Epitope** FLKEKGGL**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Donor MHC** A1, A3, B65, B8, Bw6**Keywords** HAART, ART**References** Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects – two patients recognized FLKEKGGL.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

**HXB2 Location** Nef (90–97)**Author Location** Nef**Epitope** FLKEKGGL**Subtype** A, B, C, D**Immunogen** HIV-1 infection, vaccine*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade HIV component: p17 Gag, p24 Gag**Species (MHC)** human, macaque (B8)**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].

- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  Elispot assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polypeptide region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polypeptide string Wee *et al.* [2002].

**HXB2 Location** Nef (90–97)

**Author Location** Nef (90–97)

**Epitope** FLKEKGGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A1, A3, B62, B8, Cw3, Cw7

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN- $\gamma$  secreting cells was observed, and there was no correlation between the functional avidity of a response and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a response to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (90–97 B consensus)

**Epitope** FLKEKGGL

**Epitope name** FL8

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* adeno-associated virus (AAV)

*HIV component:* gp120

**Species (MHC)** human (B8)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** dynamics, immune evasion

**References** Brainard *et al.* 2004

- HIV-1 gp120 is shown to suppress the ability of antigen-specific CTLs to migrate or remain at sites of high viral replication by concentration-dependent chemotaxis and fugetaxis. Directional T-cell movement is shown to depend on the interaction of the V2 and V3 loops with the CXCR4 receptor. X4

HIV-1 gp120 causes the migration of T-cells, including HIV-1 specific CTL, away from infected target cells, another potential mechanism for immune evasion.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (87–95)

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A03, A28, B07, B08

**Assay type** proliferation, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, memory cells, immune dysfunction

**References** Gamberg *et al.* 2004a

- HAART restores HIV specific immunity after advanced infection by increase of CD4+ and CD8+ T cell numbers after suppression of viral replication. However, HIV specific CTLs emerged only with detectable viral replication breakthroughs and were short-lived while CD4+ T-cell responses remained compromised, suggesting failure of generating stable CD8+ memory T-cells in the absence of HIV-specific T-helper responses.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** (B8)

**Keywords** binding affinity, review, escape, characterizing CD8+ T cells

**References** da Silva 2003

- Evidence of the evolutionary adaptation of HIV-1 to the specific neutralizing antibody response and CTL detection is reviewed. Both SIV and HIV epitopes are discussed, with a detailed summary of one patient's response and CTL escape in the FLKEKGGL epitope. The three C-terminal amino acids were left unchanged, and it may be due to high fitness costs as these are putatively involved in CD4 down-regulation and formation of a hydrophobic pocket in Nef. The N terminal residue is involved in binding to protein tyrosine kinases.
- Immediately after infection the susceptible epitope FLKEKGGL was found in 20/20 viral sequences. Six months later, it was only found in 4/44 sequences. The flkeNggL form was most common, 24/44 cases; it bound poorly to HLA B08 and was poorly recognized by CTL. Two minor variants were found 3/44 times, flkeEggl and flkeQggl; both bound poorly to B08, but the K->Q substitution was still well recognized. A variant flkDkggl was found in 4/44 sequences; it bound B08 moderately well, but was poorly recognized. 3 double mutants were found once each, and were not recognized by CTL: flkeNggL, flEeNggL, and flkGNggL.

**HXB2 Location** Nef (90–97)

**Author Location** Nef (89–97)

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, memory cells, characterizing CD8+ T cells

**References** Daniel *et al.* 2004

- CD4+ and CD8+ responses in chronically HIV-1 infected patients on HAART were weak with decreased polyclonality. Only 33% of patients had CD4+ T-cells that could proliferate, and only 22% had HIV-specific CD8+ T-cells T-cell responses, and those rare responses showed low perforin levels and persistent expression of CD27, indicating incomplete differentiation and loss of lytic function.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGGL

**Epitope name** FL8

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Country** United States

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding

**Keywords** immunodominance, acute/early infection, characterizing CD8+ T cells, immune dysfunction

**References** Lichterfeld *et al.* 2004a

- HIV-1 specific CD8+ T-cells in acute and long-term nonprogressive HIV-1 infection show strong ex-vivo proliferative capacities which are rapidly lost in chronic HIV-1 infection. The loss of CD8+ T-cell function is closely linked with the loss of HIV-1 specific, IL2 secreting CD4+ T-cells. The function can be rescued in vitro and in vivo by restoring the specific CD4+ T-cell help.
- Full CD8+ T-cell responses to this epitope were dependent on co-stimulation with a CD4+ T cell dependent epitope from T-cells harvested during acute infection. The CD8+ T-cell response to this epitope was immunodominant in one study individual.

**HXB2 Location** Nef (90–97)

**Author Location** (B consensus)

**Epitope** FLKEKGGGL

**Epitope name** FL8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Donor MHC** A02, A03, B08, B62, Cw10, Cw7; A11, A29, B08, B44, Cw4, Cw7; A25, A32, B08, B14, Cw7, Cw8; A01, A03, B08, B14, Cw7, Cw8

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.

- 4/9 individuals recognized this epitope, presented by HLA-B8.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Country** United Kingdom

**Assay type** Tetramer binding, T-cell Elispot, Intracellular cytokine staining

**Keywords** rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction

**References** Papagno *et al.* 2004

- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGGL

**Epitope name** FL8

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 5, FLKE $\gamma$ GGGL, was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** Nef (90–97)

**Author Location** Nef

**Epitope** FLKEKGGGL

**Epitope name** FL8

**Immunogen**

**Species (MHC)** (B8)

**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion



**References** Lichtenfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** Nef (90–97)**Author Location** Nef (90–97 HXB2)**Epitope** FLKEKGGL**Epitope name** FL8**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Donor MHC** A\*0101, A\*0201, B\*0801, B\*50, Cw\*0602, Cw\*0701**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** escape, immune evasion, viral fitness and reversion, optimal epitope**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.
- A Nef epitope FLKEeGGL (Nef-94E) presumed escape variant was transmitted from a B8 positive donor to a B8 negative recipient. FLKEgGGL, FLKgeGGL variants as well as FLKEkGGL reversions were found in the recipient subject.

**HXB2 Location** Nef (90–97)**Author Location** Nef**Epitope** FLKEKGGL**Epitope name** B8-FL8(Nef)**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (90–97)**Author Location****Epitope** FLKEKGGL**Immunogen****Species (MHC)** (B8)**Keywords** review, immunodominance, escape, vaccine antigen design**References** Altfeld & Allen 2006

- This review discusses current literature on particular CTL escape mutations that significantly impair viral fitness and argues for a concerted effort to identify these targets.
- This epitope is discussed in the context of the hierarchy of recognized HLA-B8 epitopes during acute infection (recognized by >70% of subjects).

**HXB2 Location** Nef (90–97)**Author Location****Epitope** FLKEKGGL?**Epitope name** FL8**Immunogen** HIV-1 infection**Species (MHC)** human (B8)**Country** United States, South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding**Keywords** memory cells**References** Wherry *et al.* 2006

- Cohorts of HIV-infected subjects from the US and South Africa were screened for CD8+ EliSpot responses. Tetramer assays were performed for 13 frequently targeted HIV epitopes and compared to Flu, vaccinia, and EBV epitopes assayed in non-HIV-infected subjects. HIV tetramer+ CD8 T cells expressed less CD127, and this reduction was pervasive across all epitopes and alleles tested. These results indicated impaired HIV-specific memory CD8 T cell differentiation, regardless of level of control of viremia, epitopes targeted, or HLA alleles.

**HXB2 Location** Nef (90–97)**Author Location** Nef (89–97)**Epitope** FLKEKGGL**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** immunodominance**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals that responded to SLYNTVATL reacted with seven other epitopes including this epitope previously described as presented by B8.

**HXB2 Location** Nef (90–97)**Author Location** Nef (90–97)**Epitope** FLKEKGGL**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A1, B7, B8**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs *in vivo*. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, FLKEKGGL, was found to be 0.049/day, with SE of 0.012.
- In the subject studied, a number of variants arose in the Nef epitope 90-97 (including complete epitope deletion) that were poorly recognized by CTL or escaped recognition completely.

**HXB2 Location** Nef (90–97)

**Author Location**

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0101; B\*0801, B\*1401

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- FLKEKGGL was recognized by a placebo patient after infection.

**HXB2 Location** Nef (90–97)

**Author Location**

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41

**Species (MHC)** human

**Donor MHC** A1, A10 (26); B17 (57), B8

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes

**References** Horton *et al.* 2006b

- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
- None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
- Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
- This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

**HXB2 Location** Nef (90–97)

**Author Location**

**Epitope** FLKEKGGL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, acute/early infection

**References** Lichterfeld *et al.* 2007b

- Differences in early versus chronic AIDS include a decline in CTL number accompanied by a reducing viremia. Comparative analysis of such CTLs in this study show that early infection is characterized by a different clonotypic composition and higher functional avidity of CTLs followed by their selective depletion during transition to chronic disease. The total magnitude of CTL cytokine production is lower in early infection. Intraindividual, early CTLs' functional avidity for the same epitope decreases concomitantly with a reduction in clonotypic TCR repertoire especially of strongly activated and CD127lo, CD38+, Ki-67hi CTLs while progressing to chronic infection states.
- None of the target epitopes, including this epitope FLKEKGGL seen in 4 patients, underwent sequence changes.

**HXB2 Location** Nef (90–98)

**Author Location** Nef (90–)

**Epitope** FLKEKGGL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.

- Of the most common HLA in India tested, this epitope FLKEKGGLE, is predicted to bind HLA-B8 with a binding affinity score of 1.2.

**HXB2 Location** Nef (90–100)  
**Author Location** Nef (90–100 BRU)  
**Epitope** FLKEKGGLEGL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Keywords** binding affinity, epitope processing  
**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- FLKEKGGLEGL was recognized in 8/12 (67%) of individuals with HLA A2. It was a low affinity HLA A2 binder.

**HXB2 Location** Nef (90–104)  
**Author Location** Nef (90–105 HXB2)  
**Epitope** FLKEKGGLEGLIHSQ  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** T-cell Elispot  
**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment  
**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- Responses to this peptide were detected in 16% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** Nef (92–100)  
**Author Location** Nef (92–100)

**Epitope** KEKGGLEGL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*04)  
**Country** China  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** assay standardization/improvement, optimal epitope  
**References** Wang *et al.* 2007

- HLA-A11-restricted CTL epitopes in 2 male Han Chinese subjects (one ART naive and one receiving HAART) were determined. A novel epitope was discovered and 5 other putative epitopes confirmed using 425 overlapping peptides spanning the entire HIV-1 clade B proteome. By employing intracellular cytokine staining, the authors developed a new method of mapping optimal epitopes and defining their HLA restriction efficiently. In spite of its being the most common HLA type in China, A\*11-restricted epitopes were recognized less frequently than other epitopes, and A\*11-restricted responses formed a mean of only 13% of the responses against HIV.
- This epitope, KEKGGLEGL, was detected within overlapping peptide SHFLKEKGGLEGLIYSQK.

**HXB2 Location** Nef (92–100)  
**Author Location** Nef (92–100)  
**Epitope** KEKGGLEGL

**Epitope name** KL9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*40)  
**Country** United States  
**Assay type** Intracellular cytokine staining, Other  
**Keywords** rate of progression, escape, immune evasion  
**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- A minor response was detected against an E98D variant of this epitope, KEKGGGLdGL.

**HXB2 Location** Nef (92–100)  
**Author Location** (LAI)  
**Epitope** KEKGGLEGL  
**Subtype** B  
**Immunogen**

**Species (MHC)** human (B\*4001)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*4001, B60 epitope.

**HXB2 Location** Nef (92–100)

**Author Location** Nef

**Epitope** KEKGGLEGL

**Epitope name** KL9

**Immunogen**

**Species (MHC)** (B\*4001)

**Keywords** review, immunodominance, escape, acute/early infection, early-expressed proteins, kinetics, viral fitness and reversion

**References** Lichterfeld *et al.* 2005

- This review discusses the importance of 3 factors that impact the selection of immunodominant epitopes in acute HIV infection: i) the kinetics of viral protein expression, ii) the HLA class I background of the infected individual, and iii) the autologous sequence of the infecting virus. This is 1 of 12 peptides listed as immunodominant in acute HIV-1 infection.

**HXB2 Location** Nef (92–100)

**Author Location** Nef

**Epitope** KEKGGLEGL

**Epitope name** KL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4001)

**Donor MHC** A\*0201, A\*2402, B\*4001, B\*5001, Cw03, Cw04

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** immunodominance, escape, variant cross-recognition or cross-neutralization

**References** Draenert *et al.* 2006

- HIV-specific cellular and humoral immune responses were examined in monozygotic male twins infected simultaneously with the same virus. 15 of 17 targeted epitopes were identical in the twins, including two immunodominant responses. 3 of 4 declining responses in the twins showed mutations at the same residue. Evolving antibody responses cross-neutralized the other twin's virus. The results were compared with a third brother, infected by the twins' virus 13 months after their seroconversion. The data show similarity in disease course in persons of identical genetic background infected with the same strain of HIV-1.
- This epitope, KEKGGLEGL (KL9) restricted by HLA-B\*4001, was one of two immunodominant responses.

**HXB2 Location** Nef (92–100)

**Author Location**

**Epitope** KEKGGLEGL

**Epitope name** Nef-KL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4002)

**Donor MHC** A\*0201, A\*3201, B\*4002, B\*5301, Cw\*0202, Cw\*0401

**Keywords** HAART, ART

**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Patient 01RCH59 was Hispanic, not on HAART, and had a viral load of 5100 and CD4 count of 349 – she also recognized TERQANFL, p2p7p1p6(64-70), HLA-B\*4002 and AEWDRVHPV, p24(78-86), HLA-B\*4002.
- Among HIV+ individuals who carried HLA B40, 3/5 (60%) recognized this epitope.

**HXB2 Location** Nef (92–100)

**Author Location** Nef (92–100)

**Epitope** KEKGGLEGL

**Immunogen**

**Species (MHC)** human (B\*4002)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Nef (92–100)

**Author Location** Nef

**Epitope** KEKGGLEGL

**Epitope name** B40-KL9(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B40)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (92–100)

**Author Location** Nef

**Epitope** KEKGGLEGL

**Epitope name** KL-9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B40)

**Assay type** Other

**Keywords** escape, TCR usage, immune evasion

**References** Yu *et al.* 2007b

- The dependence of TCR clonotype recruitment on genetic background was determined by studying monozygotic twins infected with the same HIV-1 strain. After an early, initial correlation in the magnitude, specificity and immunodominance of CTL response [Draenert *et al.* *J. Exp. Med.* 203:529-539(2006)], subsequent disease was mixed with respect to CTL epitopes' mutational escape. TCR alpha and beta chain repertoires were analyzed and it was found that their clonotypes in HIV-specific CTLs were broadly heterogeneous for both concordant and discordant epitope sequence evolution between the twins. Therefore initial TCR recruitment appears to be an entirely random process independent of genetic background of the infected individual.
- This epitope, KL9, showed concordant epitope evolution between the twins, but both alpha and beta TCR chains recruited were entirely different between them.

**HXB2 Location** Nef (92–100)

**Author Location**

**Epitope** KEKGGLEGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B40)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- In addition to its known HLA association (B40), an additional HLA (B49) was statistically predicted to be associated with this epitope.

**HXB2 Location** Nef (92–100)

**Author Location** Nef (90–98 SF2)

**Epitope** KEKGGLEGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.

- Number of HLA-B60+ individuals that had a CTL response to this epitope broken down by group: 2/2 group 1, 1/1 group 2, and 0/0 group 3.

**HXB2 Location** Nef (92–100)

**Author Location** Nef (SF2)

**Epitope** KEKGGLEGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**References** Altfeld *et al.* 2000

- This epitope was the dominant B60 (encoded by B\*4001) response in 6/8 HLA-B60 individuals, and recognized in all eight.
- This epitope was also recognized two expressing HLA-B61 individuals (B61 is usually encoded by B\*4002, but this study did not distinguish between B\*4002, B\*4003, B\*4004, B\*4006, and B\*4008)
- ELISPOT was a rapid an effective method that was used to define five novel B60 epitopes.
- HLA-B60 is present in 10-20% of the Caucosoid population and B60/B61 are very common in Asian populations.

**HXB2 Location** Nef (92–100)

**Author Location** Nef

**Epitope** KEKGGLEGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Keywords** epitope processing

**References** Cao *et al.* 2002

- KM is a B60 restricted CTL clone that recognizes KEKGGLEGL.
- CTL could be activated by a fusion protein of an HIV protein and anthrax lethal factor (LFn-HIV) that promotes antigen presenting cell uptake of exogenous protein and allows processing through the MHC class I pathway. This strategy for CTL detection could allow antigen presentation without generation of cells by the standard methods of using live viral vectors carrying a protein, or by loading the cells with peptides and by-passing processing.

**HXB2 Location** Nef (92–100)

**Author Location** Nef (92–100 NL-43)

**Epitope** KEKGGLEGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Keywords** class I down-regulation by Nef, escape

**References** Ali *et al.* 2003

- NL43 was passaged in the presence of Nef KEKGGLEGL-specific CTL clones STD11 and KM3, giving rise to rapid selection of escape mutations, including E93G, E93K, K94N+G99R, G95R+G99R, E98K, E98D, G99R, G99E, L100P, and L100I; insertions, deletions, frameshifts and an early stop codon. 34/36 (94%) of sequences carried mutations in the epitope by seven days, 36/36 (100%) by 14 days.
- NL43 was also passaged in the presence of a Nef TQGYFPDQWNY-specific CTL clone. 7/15 clones had a frameshifting or stop codon introduced by one week; F121T was also observed. The most common escape mutation for both Nef epitopes was an early stop codon at position 91.

- Several mutations selected by KEKGGLEGL-specific CTL were shown to impair the down regulation of class I MHC by Nef, in particular E93G, E93K, and a truncation mutation at position 51.
- Nef deletion mutants increased 100-fold NL-43 susceptibility to inhibition by CTL specific for epitopes in other proteins, the A2 epitopes ILKEPVHGV in RT and SLYNTVATL in p17 Gag.

**HXB2 Location** Nef (92–100)

**Author Location** Nef

**Epitope** KEKGGLEGL

**Epitope name** KL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Donor MHC** A2, A24, B38, B60, Cw12, Cw2

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), early treatment

**References** Montefiori *et al.* 2003

- HIV-1 + patient AC10 underwent early HAART treatment, which was discontinued 1.5 years later. At this timepoint potent NAb responses against autologous virus were detected. Treatment interruption initially induced weak CD8+ responses directed against 5 epitopes. By days 873d and 923d the CTL response had broadened to target 22 epitopes; of these six were fully characterized. Eventually the virus escaped the NAb response, but escape was not accompanied by a rise in viral load, and the authors suggest the virus was contained by the CTL response.

**HXB2 Location** Nef (92–100)

**Author Location** Nef (92–100 NL43)

**Epitope** KEKGGLEGL

**Epitope name** KL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Assay type** Chromium-release assay, CTL suppression of replication

**Keywords** escape

**References** Yang *et al.* 2003a

- Virus was cultured in the presence of CTL lines specific for 5 different epitopes (SLYNTVATL, ILKEPVHGV, IEIKDTKEAL, SEGATPQDL, and KEKGGLEGL) to study the emergence of escape mutations. Escape varied between clones for the same epitope, and between different epitopes. Gag and RT epitope escape, if it occurred at all, tended to be monoclonal and within the epitope, indicating strong fitness constraints, while the Nef epitope escape was rapid, polyclonal, and sometimes the result of upstream frameshifts.
- Two cloned CTL lines recognized KEKGGLEGL, STD11 and KM3. Highly resistant clones emerged after a single round of passage with both CTL clones, and multiple substitutions accrued including frameshifts and stop codons, reflecting the dispensability of Nef in viral culture.
- The following epitope variants were observed after passaging with clone STD11 for one week: kekggegl, kKkggegl, and 12/20 frameshifts and 1 early stop. By two weeks, a more complex polyclonal mixture was observed including:

kekggegl, kKkggegl kekggeP, kekggeEl, kekggeRl, kekRgeRl, keNggeRl, and 11/22 frameshifts.

**HXB2 Location** Nef (92–100)

**Author Location** Nef (92–100)

**Epitope** KEKGGLEGL

**Epitope name** Nef KL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, TCR usage, characterizing CD8+ T cells

**References** Yang *et al.* 2003b

- Killing efficiency of CTLs and their ability to suppress viral replication is shown to depend more on epitope specificity than to antigenic avidity. Different clones recognizing the same epitope had similar killing efficiency despite their variation in avidity. Nef specific CTL clones tended to be most inhibitory, followed by Gag, then by RT specific clones, regardless of avidity.
- 2/14 CTL T-cell clones tested were specific for Nef KL9. Under conditions of excess peptide (100ug/ml), there was no difference in their lytic potential; all possessed similar effector capacity. Avidity was measured as the sensitizing dose of peptide required for 50% of maximal killing (SD50), which varied from 20 pg/ml to 100 ng/ml, over four orders of magnitude for all 14 epitopes. The SD50 range for Nef KL9 was 20-30 pg/ml, both high avidity. These clones were among the most efficient at inhibiting viral replication in the set tested, but because of the general lack of correlation between avidity and viral inhibition efficiency in this study, the authors attribute other reasons to Nefs ability to inhibit viral replication that pertain to presentation like kinetics and expression levels.

**HXB2 Location** Nef (92–100)

**Author Location** (B consensus)

**Epitope** KEKGGLEGL

**Epitope name** KL10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60)

**Donor MHC** A03, B14, B60, Cw3, Cw7

**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells

**References** Lichterfeld *et al.* 2004c

- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.

- 1/9 individuals recognized this epitope; the authors write that it is presented by HLA-B40 in their Table 1, but the subject that recognizes it, AC05, is HLA-B60, so we assume they meant B60.

**HXB2 Location** Nef (92–100)

**Author Location** Nef (92–100)

**Epitope** KEKGGLEGL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B60, B61)

**Keywords** immunodominance

**References** Day *et al.* 2001

- No immunodominant responses were detected to five B61-restricted epitopes tested.
- All five B60-restricted epitopes were reactive in another subject, and the B60-restricted responses together contributed over one-third of the total CTL response.

**HXB2 Location** Nef (92–105)

**Author Location** Nef

**Epitope** KEKGGLEGLVYSQK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A28, A29, B14, B44, Cw8

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- Novel unmapped epitope. There was a V->A change KEKGGLEGLaYSQK over time in an individual that reacted with this peptide.

**HXB2 Location** Nef (92–112)

**Author Location** Nef (SF2)

**Epitope** KEKGGLEGLIHSQRRQDILD

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

**HXB2 Location** Nef (92–112)

**Author Location** Nef (SF2)

**Epitope** KEKGGLEGLIHSQRRQDILD

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Altfeld *et al.* 2000

- This epitope was mapped by ELISPOT in a study identifying new HLA-B60 epitopes, and was one of the epitopes presented by another HLA molecule in an HLA-B60 individual.
- The response to the peptide was CD8 dependent, but the HLA presenting molecule and optimal epitope were not determined.

**HXB2 Location** Nef (93–106)

**Author Location** Nef (93–106 BRU)

**Epitope** EKGGLEGLIHSQRR

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1, B8)

**References** Hadida *et al.* 1992

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients.

**HXB2 Location** Nef (93–107)

**Author Location** Nef

**Epitope** EKGGLEGLIYSQKRQ

**Epitope name** nef-5162

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISPOT studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, EKGGLEGLIYSQKRQ was mutated in the daughter D2 isolate to EmGGLdGLIYSQrRQ.

**HXB2 Location** Nef (96–104)

**Author Location** Nef (96–)

**Epitope** GLEGLIYSK

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope GLEGLIYSK, is predicted to bind HLA-A1 with a binding affinity score of 36.

**HXB2 Location** Nef (96–113)

**Author Location** Nef

**Epitope** GLEGLIYSQKRQDILDLDLW

**Epitope name** NEF-14

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [*J. Virol.* 78:2187-2200 (2004)].
- This peptide, GLEGLIYSqKRQdILDLDLW differs from the consensus C sequence GLEGLIYSkKRQeILDLDLW at 2 amino acid positions, i.e. by 11.1%.

**HXB2 Location** Nef (97–111)

**Author Location** Nef (97–111)

**Epitope** LEGLIYSKKRQEILD

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanaans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.

- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Nef (101–109)

**Author Location** Nef (101–109)

**Epitope** IYSQKRQDI

**Subtype** B

**Immunogen** HIV-1 infection, peptide-HLA interaction

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** immunodominance

**References** Rolland *et al.* 2007b

- Resemblance between viral and host peptides may preclude immune reactivity against such epitopes. This was shown using ELISpot to test recognition against the entire viral genome in 314 HIV-infected subjects. Also, 944 overlapping Nef variants were tested for 30 patients. This inverse relationship between similarity of HIV epitope to host proteome and its immunogenicity has implications in vaccine design.
- Other factors, however, like entropy effects and forbidden residue usage or even hydrophobicity or disorder prediction scores were more influential than this similarity to self, with regards to immunogenicity of HIV-1. Also, forbidden aa ratios at the C-terminus of CTL epitopes and similarity to host proteins are positively correlated. Low disorder peptides elicit broader CTL responses and are better recognized.
- This HIV-1 epitope, IYSQKRQDI, is similar to human protein Ig heavy chain variable region, sequence tYSQKfQDI.

**HXB2 Location** Nef (101–115)

**Author Location** Nef (101–115)

**Epitope** IYSQKRQDILDLDLWIY

**Epitope name** KY11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw07)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide, IYSQKRQDILDLDLWiY, is a variant of the consensus peptide IYSQKRQDILDLDLVY.

**HXB2 Location** Nef (101–115)

**Author Location**



- Epitope** IHSQRRQDILDWY  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag-Pol, gp120, gp41  
**Species (MHC)** human  
**Donor MHC** A1, A2; B38, B8  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** vaccine-induced epitopes  
**References** Horton *et al.* 2006b
- T cell responses during early infection in individuals previously enrolled in HIV vaccine trials were compared with those of nonvaccinated subjects.
  - None of the breakthrough infections possessed vaccine-induced T-cell responses preinfection and 85-86% of vaccinees and nonvaccinees with primary infection developed T-cell responses postinfection, indicating that vaccinees' ability to mount T-cell response postinfection is not compromised by previous immunization.
  - Breakthrough subjects recognized 43 T-cell epitopes, 8 of them novel, and 25% were present in the vaccine.
  - This epitope was not contained in the vaccine, the vaccinated patient recognized it after infection.

- HXB2 Location** Nef (102–110)  
**Author Location** Nef (102–110)  
**Epitope** HSQRRQDIL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*24, B\*37, Cw\*0401, Cw\*0602)  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, immunodominance  
**References** Thakar *et al.* 2005
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
  - 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
  - 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
  - Epitope HSQRRQDIL showed some conservation to subtype B.

- HXB2 Location** Nef (102–110)  
**Author Location** Nef (102–)  
**Epitope** YSKKRQEIL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B8)  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons

- References** Kumar *et al.* 2006a
- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
  - Of the most common HLA in India tested, this epitope YSKKRQEIL, is predicted to bind HLA-B8 with a binding affinity score of 80.

- HXB2 Location** Nef (102–115)  
**Author Location** Nef (102–115 LAI)  
**Epitope** HSQRRQDILDWY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** review, escape  
**References** Goulder *et al.* 1997e; Goulder *et al.* 1997a
- HLA identical sibling hemophilic brothers were both infected with the same batch of factor VIII.
  - They were tested 6-8 years after infection; one had a strong response to this peptide, the other did not.
  - Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

- HXB2 Location** Nef (102–115)  
**Author Location** Nef (100–113)  
**Epitope** HSQRRQDILDWY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Country** Spain  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004
- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
  - 5/7 patients recognized this epitope.

- HXB2 Location** Nef (102–121)  
**Author Location** Nef (101–120 SF2)  
**Epitope** HSQRRQDILDLIYHTQGYF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997a
- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
  - Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
  - Two of these 11 had CTL response to this peptide.
  - The responding subjects were HLA-A2, A3, B8, B62 and HLA-A2, B21.

- HXB2 Location** Nef (103–117)  
**Author Location** Nef (103–117)

**Epitope** SQRRQDILDWVYHT**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (Cw07)**Donor MHC** B\*1503, B35, B7 supertype, Cw7**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** computational epitope prediction, vaccine-induced epitopes**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope, SQRRQDILDWVYHT, varies at position 3 from the consensus peptide KRQDILDWVYHTQG.

**HXB2 Location** Nef (103–117)**Author Location** Nef**Epitope** SKKRQEILDWVYHT**Subtype** A, D**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A\*0202, A\*3002, B\*5703, B\*5802; A\*6801, A\*7401, B\*0702, B\*3501**Country** Uganda**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, variant cross-recognition or cross-neutralization**References** Barugahare *et al.* 2005

- T-cell immune responses were examined in HIV-1 infected Ugandans. Similar levels of cross-clade responses for Gag, Env and Nef were observed. Higher frequencies of responses in conserved regions were found for Gag within a single clade, while areas with higher viral sequence variation had fewer detectable responses. Differential interclade sequence homologies between the Gag regions did not affect the respective level of cross-clade recognition.
- The sequence contains a previously-defined epitope (KRQEILDWVY) of unknown HLA restriction. The viral sequence from the subjects that recognized the peptide was skkrqKildwvYnt.

**HXB2 Location** Nef (103–127)**Author Location** Nef (103–127 PV22)**Epitope** SQRRQDILDWVYHTQGYFPDQWNY**Immunogen** HIV-1 infection**Species (MHC)** human (B13)**References** Jassoy *et al.* 1993

- HIV-1 specific CTLs release  $\gamma$ -IFN, and  $\alpha$ - and  $\beta$ -TNF.

**HXB2 Location** Nef (103–127)**Author Location** Nef (103–127)**Epitope** SQRRQDILDWVYHTQGYFPDQWNY**Epitope name** SQR**Immunogen** HIV-1 infection**Species (MHC)** human (B13)**Keywords** HAART, ART, acute/early infection**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- The only study subject out of eight that was HLA B13+ recognized this epitope.
- Patient SC9 (HLA A1/2, B8/13, Cw0/0701, DR2/11, DQ6/7) had a CTL response against epitopes FLKEKGGL, ILKEPVHGV, SQRRQDILDWVYHTQGYFPDQWNY, and GEIYKRWII peptides and all responses declined during therapy initiated at day 390 but were restored when therapy became intermittent.

**HXB2 Location** Nef (104–112)**Author Location** Nef (104–112)**Epitope** QRRQDILD**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*37, Cw\*0602)**Country** India**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, computational epitope prediction, immunodominance**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope QRRQDILD showed some conservation to subtypes A and B.

**HXB2 Location** Nef (104–121)**Author Location** Nef**Epitope** QKRQDILDWVYHTQGYF**Epitope name** NEF-15**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Country** China**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, immunodominance**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm et al. [J. Virol. 78:2187-2200 (2004)].
- This peptide, qKRQdILDWVYHTQGYF differs from the consensus C sequence kKRQeILDWVYHTQGYF at 2 amino acid positions, i.e. by 11.1%.

**HXB2 Location** Nef (104–121)

**Author Location** Nef

**Epitope** QKRQDILDWVYHTQGYF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, QKRQDILDWVYHTQGYF, had an overall frequency of recognition of 26% - 28.8% AA, 26.9% C, 25% H, 19% WI. This peptide is included in a 54 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region II', QKRQDILDWVYHTQGYFPDWQNYTPGP-GIRYPLTFGWCFKLVPEPEKVEEAN, a 54 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** Nef (105–113)

**Author Location** Nef (105–)

**Epitope** KRQEILDW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*2702, B\*2705)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope KRQEILDW, is predicted to bind HLAs - B\*2702 and B\*2705 with binding affinity scores of 300 and 600.

**HXB2 Location** Nef (105–114)

**Author Location** Nef (105–114 LAI)

**Epitope** RRQDILDWLI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*2705)

**Keywords** rate of progression

**References** Goulder *et al.* 1997c

- Defined as optimal epitope from within reactive peptide HSQRRQDILDWYHTQGYF [Nef(102-121 LAI)]
- HLA-B\*2705 is associated with slow HIV disease progression.
- The HLA-B\*2705 binding motif includes R at position 2, and L in the C-term position.

**HXB2 Location** Nef (105–114)

**Author Location** Nef (105–114 LAI)

**Epitope** RRQDILDWLI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*2705)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*2705 epitope.

**HXB2 Location** Nef (105–114)

**Author Location** Nef (105–114 SF2)

**Epitope** RRQDILDWLI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B27+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 0/0 group 2, and 1/1 group 3.

**HXB2 Location** Nef (105–114)

**Author Location** Nef (105–114)

**Epitope** RRQDILDLWI

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Day *et al.* 2001

- B27-restricted CTL response was strongest to this epitope in one individual.

**HXB2 Location** Nef (105–114)

**Author Location**

**Epitope** RRQDILDLWI

**Epitope name** Nef-RII10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B27)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B27, 1/2 (50%) recognized this epitope.

**HXB2 Location** Nef (105–115)

**Author Location**

**Epitope** RRQDILDLWVY

**Epitope name** RY11

**Immunogen**

**Species (MHC)** human (B18)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B18 epitope.

**HXB2 Location** Nef (105–115)

**Author Location** Nef (105–115)

**Epitope** RRQDILDLWVY

**Epitope name** RY11

**Immunogen** HIV-1 infection

**Species (MHC)** human (C\*07)

**Assay type** CTL suppression of replication

**Keywords** class I down-regulation by Nef

**References** Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Nef epitope RRQDILDLWVY-recognizing HLA-C restricted CTLs were unaffected by Nef.

**HXB2 Location** Nef (105–115)

**Author Location** Nef (105–115)

**Epitope** KRQDILDLWVY

**Epitope name** KY11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*07)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 4 additional variants of this epitope, KRQDILDLWVY, were determined using PTE-B - rRQDILDLWVY, KRQeILDLWVY, rRQeILDLWiY, and KRQDILDLWiY. Only the consensus and last variant KRQDILDLWiY were actually found as patient autologous sequences.

**HXB2 Location** Nef (105–115)

**Author Location** (C consensus)

**Epitope** KRQDILDLWVY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0701)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the R2 residue of KRQDILDLWVY are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** Nef (105–115)

**Author Location** Nef

**Epitope** KRQEILDLWVY

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0701)

**Country** Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization  
**References** Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRF-FKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequence kKRQEILDLWVYhtq is associated with HLA-Cw\*0701 and contains the epitope KRQEILDLWVY.

**HXB2 Location** Nef (105–115)

**Author Location** (C consensus)

**Epitope** KRQEILDLWVY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0701, Cw\*0702)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Nef (105–115)

**Author Location** (C consensus)

**Epitope** KRQDILDLWIY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0702)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Optimal epitope.

**HXB2 Location** Nef (105–115)

**Author Location**

**Epitope** RRQDILDLWIY

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw07)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope RRQDILDLWIY elicited a magnitude of response of 460 SFC with a functional avidity of 0.0005nM.

**HXB2 Location** Nef (105–115)

**Author Location** Nef (105–115)

**Epitope** RRQDILDLWIY

**Epitope name** Cw7-RY11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- AC-06 was homozygous at all three class I alleles (A3, B7, Cw7), and was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 response to RRQDILDLWIY restricted by HLA-Cw7.

**HXB2 Location** Nef (105–115)

**Author Location** Nef (105–115)

**Epitope** KRQEILDLWVY

**Immunogen**

**Species (MHC)** human (Cw7)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this as a Cw7 epitope. Variant rRQDILDLWIY also noted.

**HXB2 Location** Nef (105–115)

**Author Location** Nef (C consensus)

**Epitope** KKQEILDLWVY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw7)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- People who carried Cw07 often carried a variant of this epitope, while the susceptible form of the epitope was highly conserved among those who did not.

**HXB2 Location** Nef (105–119)

**Author Location** Nef (105–119 HXB2)

**Epitope** RRQDILDLWIYHTQG

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2–42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 19% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** Nef (106–114)

**Author Location** Nef (106–114)

**Epitope** RQDILDLWI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*24, B\*37, Cw\*0602)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5

immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.

- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope RQDILDLWI showed some conservation to subtype B.

**HXB2 Location** Nef (106–114)

**Author Location** Nef (106–114)

**Epitope** RQDILDLWV

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*13)

**Donor MHC** A\*0301, A\*3001, B\*1301, B\*1402, Cw\*0602, Cw\*0802

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** epitope processing, immune evasion, viral fitness and reversion, HLA associated polymorphism

**References** Honeyborne *et al.* 2007

- To determine whether HLA-B\*13-restricted CTL responses could partially explain low viremic loads in patients, a cohort of chronic C-clade infected subjects was studied. 6 novel B\*13-restricted CTL epitopes were defined from both C- and B-clade viruses, 3 of which were within Gag. B\*13-restricted CTL responses correlated with lower viremia, with most immunity targeted against Gag epitopes (p15, p17, p24). Gag epitope escape variants may exact a high viral fitness cost, mutations being seen within and around the optimal epitope.

**HXB2 Location** Nef (106–114)

**Author Location** Nef (106–114)

**Epitope** RQDILDLWI

**Epitope name** RI9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B13)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, escape, variant cross-recognition or cross-neutralization, optimal epitope

**References** Harrer *et al.* 2005

- An HLA-B13-restricted optimal epitope was defined in Nef, RI9. The frequency of CTLs specific for this epitope in B13-positive patients exceeded the number of CTLs against other epitopes, indicating that this is a dominant epitope in B13-positive subjects. Three B13-positive patients who had an immunodominant response to this epitope were good controllers of their infection, with low viral loads over long periods.
- In B13-positive patients with a previous diagnosis of AIDS, an RrDILDLWI escape variant was found.

- This is a well conserved epitope but natural variants were tested. Peptide titration experiments indicate a V91 RQDILDLWv variant and RQDILDLWI are equally well recognized. Other natural substitutions are less well recognized: RkDILDLWI, RQeILDLWI, aQDILDLWI, RQaILDLWI, RrDILDLWv.

**HXB2 Location** Nef (106–114)

**Author Location** Nef (106–114)

**Epitope** RQDILDLWI

**Immunogen**

**Species (MHC)** human (B13)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an B13 epitope. Variant RQDILDLWv also noted.

**HXB2 Location** Nef (106–115)

**Author Location** (LAI)

**Epitope** RQDILDLWIY

**Subtype** B

**Immunogen**

**Species (MHC)** human (B\*0702)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008; Goulder 1999

- C. Brander notes this is a B\*0702 epitope.

**HXB2 Location** Nef (106–115)

**Author Location** Nef

**Epitope** RQDILDLWIY

**Epitope name** B7-RY10(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (106–115)

**Author Location** Nef

**Epitope** RQDILDLWVY

**Epitope name** RY10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw7)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 9, RQDILDLWiY, was found in the most polymorphic residue in the epitope.

**HXB2 Location** Nef (106–120)

**Author Location** Nef (106–120)

**Epitope** RQEILDLWVYHTQGY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw07)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope, RQEILDLWVYHTQGY, varies at position 3 from the consensus peptide KRQDILDLWVYHTQG.

**HXB2 Location** Nef (107–115)

**Author Location** (C consensus)

**Epitope** QDILDLWIY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*18)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in the D2 residue of QDILDLWIY are associated with the presence of the HLA presenting molecule in the host.
- QDILDLWIY not optimized.

- HXB2 Location** Nef (107–115)  
**Author Location** Nef (107–115)  
**Epitope** QDILDLWIY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*37, Cw\*0602)  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, immunodominance  
**References** Thakar *et al.* 2005
- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
  - 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
  - 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
  - Epitope QDILDLWIY showed some conservation to subtype B.

- HXB2 Location** Nef (108–115)  
**Author Location**  
**Epitope** DILDLWIY  
**Epitope name** Nef-DY8  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw\*0701)  
**Donor MHC** A\*2601, A\*3303, B\*5801, B\*8201, Cw\*0302, Cw\*0701  
**Keywords** HAART, ART  
**References** Sabbaj *et al.* 2003
- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
  - 24 epitopes were described; 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
  - Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
  - Subject 03RCH40 was African American, had a viral load of 2500, CD4 count of 372, was not on HAART, and also recognized the epitope ETKLGKAGY, RT(449-457), A\*2601.
  - Among HIV+ individuals who carried HLA Cw07, 2/18 (11%) recognized this epitope.

- HXB2 Location** Nef (108–115)  
**Author Location** Nef (108–115)  
**Epitope** DILDLWIY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (Cw7)  
**Donor MHC** A1A1, B14, B8, Cw7, Cw8  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- CTL epitope responses were mapped in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized tended not to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently recognized than A1, A2, A30, and A44.

- HXB2 Location** Nef (109–117)  
**Author Location** Nef (109–)  
**Epitope** ILDLWVYHT  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*0205)  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons  
**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope ILDLWVYHT, is predicted to bind HLA-A\*0201 with a binding affinity score of 11.655 and HLA-A\*0205 with a predicted score of 1.36.

- HXB2 Location** Nef (109–117)  
**Author Location** Nef (109–117)  
**Epitope** ILDLWIYHT  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*03)  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, immunodominance  
**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be



recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.

- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope ILDLWIYHT showed some conservation to subtype B.

**HXB2 Location** Nef (112–126)

**Author Location** Nef (112–126)

**Epitope** LWVYHTQGYFPDWQN

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanaans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 28 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Nef (112–127)

**Author Location** Nef

**Epitope** LWVYHTQGYFPDWQNY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.

- This immunodominant, frequently targeted overlapping peptide, LWVYHTQGYFPDWQNY, had an overall frequency of recognition of 30% - 25.4% AA, 38.5% C, 31.8% H, 28.6% WI. This peptide is included in a 54 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region II', QKRQDILDLWVYHTQGYFPDWQNYTPGP-GIRYPLTFGWCFKLVPEPEKVEEAN, a 54 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** Nef (112–133)

**Author Location** Nef (111–132)

**Epitope** LWIYHTQGYFPDWQNYTPGPGV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** Nef (112–133)

**Author Location** Nef (111–132 SF2)

**Epitope** LWIYHTQGYFPDWQNYTPGPGV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Four of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A2, B21; HLA-A1, A3, B7, B15; HLA-A2, A26, B7, B38.

**HXB2 Location** Nef (112–133)

**Author Location** Nef (111–132 SF2)

**Epitope** LWIYHTQGYFPDWQNYTPGPGV

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** Nef (113–121)

**Author Location** Nef (111–119)

**Epitope** WIYHTQGYF

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 3/13 patients recognized this epitope.

**HXB2 Location** Nef (113–121)  
**Author Location** Nef (113–121)  
**Epitope** WIYHTQGYF  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*35, Cw\*0401, Cw\*0602)  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, immunodominance  
**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope WIYHTQGYF from the central region of Nef showed a 20–30% conservation with subtype B. Its HLA specificities are with B\*35, Cw\*04 and Cw\*06.

**HXB2 Location** Nef (113–125)  
**Author Location** Nef (113–125 BRU)  
**Epitope** WIYHTQGYFPDWQ  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B17)  
**References** Culmann *et al.* 1989  
 • Nef CTL clones from HIV+ donors.

**HXB2 Location** Nef (113–127)  
**Author Location** Nef (128–142)  
**Epitope** WIYHTQGYFDPWQNY  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** subtype comparisons  
**References** Guimarães *et al.* 2002

- Nef sequences were obtained from Brazilians to study epitope diversity in this geographic region – WIYHTQGYFDPWQNY displayed an (H) to (N) substitution in Brazilian Nef-gene subtype C samples, and this substitution is often found in other subtypes tested.

**HXB2 Location** Nef (113–128)  
**Author Location** Nef (113–128 BRU)  
**Epitope** WIYHTQGYFPDWQNYT

**Immunogen** HIV-1 infection  
**Species (MHC)** human (A1)  
**References** Hadida *et al.* 1992

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients.

**HXB2 Location** Nef (113–128)  
**Author Location** Nef (113–128 LAI)  
**Epitope** WIYHTQGYFPDWQNYT  
**Epitope name** N2  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A1)  
**Keywords** HAART, ART  
**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** Nef (114–127)  
**Author Location** Nef  
**Epitope** VYHTQGYFPDWQNY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Jubier-Maurin *et al.* 1999

**HXB2 Location** Nef (115–125)  
**Author Location** Nef (115–125 BRU)  
**Epitope** YHTQGYFPDWQ  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B17)  
**References** Culmann *et al.* 1991  
 • Nef CTL clones from HIV+ donors.

**HXB2 Location** Nef (115–129)  
**Author Location** Nef (115–129 HXB2)  
**Epitope** YHTQGYFPDWQNYTP  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** T-cell Elispot  
**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment  
**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.

- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 22% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** Nef (116-124)  
**Author Location** Nef (116-124)  
**Epitope** HTQGYFPDW  
**Immunogen**  
**Species (MHC)** human (B\*57)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Nef (116-124)  
**Author Location** Nef (116-124)  
**Epitope** HTQGYFPDW  
**Immunogen**  
**Species (MHC)** human (B57)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Nef (116-124)  
**Author Location**  
**Epitope** HTQGYFPDW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B57)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** assay standardization/improvement, epitope processing  
**References** Draenert *et al.* 2004a

- 96% of optimally defined epitopes have one of only nine amino acids serving as the C-terminal anchor position. Seven amino acids are never found in this position and four are only present in 4% of cases. CD8 T-cell response to an epitope is shown to be best detected when the epitope is situated at the C-terminal end of a longer peptide, and authors suggest that Elispot reagents would be better designed if peptides ended on known C-terminal anchors.
- HTQGYFPDW is suggested to be the optimal epitope instead of HTQGYFPDWQ since Gln is not described as a C-terminal anchor residue in any of the other optimally defined epitopes. HTQGYFPDW was also found to be recognized at two times lower peptide concentrations than HTQGYFPDWQ.

**HXB2 Location** Nef (116-124)  
**Author Location** Nef (116-124)

**Epitope** HTQGYFPDW

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A\*3001, A\*66, B\*4201, B\*5802, Cw\*0602, Cw\*1701; A\*66, A\*68, B\*57, B\*5802, Cw\*0602, Cw\*0701

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection

**References** Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- HTQGYFPDW is the C consensus form of the epitope; the autologous form in the mother was HTQGfFPDW, and this was transmitted to her infant. By 33 weeks a new dominant form of the epitope had emerged in the infant: nTQGfFPDW.

**HXB2 Location** Nef (116-124)

**Author Location** Nef

**Epitope** HTQGYFPDW

**Epitope name** B57-HW9(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (116-124)

**Author Location** Nef

**Epitope** HTQGYFPDW

**Epitope name** HW9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells

**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.
- While 2 mothers carried the form HTQGYFPDW, their children carried the escape H1N variant nTQGYFPDW.

**HXB2 Location** Nef (116–124)

**Author Location** Nef (116–124 BRU)

**Epitope** HTQGYFPDW

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B58)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 0/9 CRF02\_AG-infected Ivoirians, and 1/9 B-infected French subject
- HTQGYFPDW was invariant in 5 B clade infected individuals, including the one that recognized the epitope. It varied in 4/8 CRF02 Ivoirian infections.

**HXB2 Location** Nef (116–125)

**Author Location**

**Epitope** HTQGYFPDWQ

**Epitope name** HQ10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B\*57-restricted optimal epitope HTQGYFPDWQ was tested for immune response.

**HXB2 Location** Nef (116–125)

**Author Location** Nef (116–125)

**Epitope** HTQGYFPDWQ

**Epitope name** HQ10

### Subtype B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Country** Switzerland

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** rate of progression, HLA associated polymorphism

**References** Frater *et al.* 2007

- To study whether CTL responses restricted by "good" HLA I molecules exert stronger immune selection than "other" HLA I molecules, 54 and 70 optimal epitopes within HIV-1 Gag, Pol and Nef genes for Caucasian and African cohorts were tested in patients over a mean of 14 months. "Good", advantageous HLA allele-restricted epitopes were much more polymorphic than epitopes restricted by "other", non-advantageous HLA in patients, suggesting that benefits associated with HLA Class I alleles of elite controllers of disease progression are epitope-specific. Such "driver" epitopes with high polymorphism had high frequency of immune response, allowing them to be ranked for recognition and polymorphism.
- Patients with higher proportions of mutated epitopes also showed lower plasma viral loads, and mean epitope variability correlated negatively with relative hazard of disease progression.
- Variant nTQGYFPDWQ at position 1 was found in 100% of HLA-matched patients and in 28.8% of HLA-unmatched patients.

**HXB2 Location** Nef (116–125)

**Author Location** Nef (116–125)

**Epitope** HTQGYFPDWQ

**Epitope name** HQ10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CTL suppression of replication

**Keywords** class I down-regulation by Nef

**References** Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Early protein Nef epitope HTQGYFPDWQ-recognizing CTLs were less affected by Nef.

**HXB2 Location** Nef (116–125)

**Author Location** Nef (116–125)

**Epitope** HTQGYFPDWQ

**Epitope name** nefHQ10

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Country** United Kingdom, Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** TCR usage, structure, characterizing CD8+ T cells

**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.

- In addition, immunodominancy of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFN-PEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** Nef (116–125)

**Author Location** Nef (116–125 BRU)

**Epitope** HTQGYFPDWQ

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** subtype comparisons, optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5701 epitope.
- Subtype of B57 not determined.

**HXB2 Location** Nef (116–125)

**Author Location** Nef (116–125)

**Epitope** HTQGYFPDWQ

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- One of the A2+ individuals was HLA A\*0201, A1, B57 and responded to four B57 epitopes and two others.

**HXB2 Location** Nef (116–125)

**Author Location** Nef (116–125 BRU)

**Epitope** HTQGYFPDWQ

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Culmann *et al.* 1991

- Nef CTL clones from HIV+ donors, optimal peptide mapped.

**HXB2 Location** Nef (116–125)

**Author Location** Nef (116–125)

**Epitope** HTQGYFPDWQ

**Epitope name** HTQ

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Keywords** HAART, ART, acute/early infection

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B57+

**HXB2 Location** Nef (116–125)

**Author Location**

**Epitope** HTQGYFPDWQ

**Epitope name** Nef-HQ10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 0/5 (0%) recognized this epitope.

**HXB2 Location** Nef (116–125)

**Author Location** Nef (114–123)

**Epitope** HTQGYFPDWQ

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - INF $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 7 patients recognized this epitope.

**HXB2 Location** Nef (116–125)

**Author Location** Nef

**Epitope** HTQGYFPDWQ

**Epitope name** HQ10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - INF $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 1, nTQGYFPDWQ, was found in the most polymorphic residue in the epitope.

**HXB2 Location** Nef (116–125)

**Author Location**

**Epitope** HTQGYFPDWQ

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** Nef (116–125)

**Author Location** Nef

**Epitope** HTQGYFPDWQ

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B63)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 30% of B63-positive subjects and 35% of B57/58-positive subjects.

**HXB2 Location** Nef (117–127)

**Author Location** Nef (117–127 LAI)

**Epitope** TQGYFPDWQNY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1501)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1501 epitope.

**HXB2 Location** Nef (117–127)

**Author Location** Nef (117–127 NL-43)

**Epitope** TQGYFPDWQNY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1501)

**Keywords** class I down-regulation by Nef, escape

**References** Ali *et al.* 2003

- NL43 was passaged in the presence of Nef KEKGGLEGL-specific CTL clones STD11 and KM3, giving rise to rapid selection of escape mutations, including E93G, E93K, K94N+G99R, G95R+G99R, E98K, E98D, G99R, G99E, L100P, and L100I; insertions, deletions, frameshifts and an early stop codon. 34/36 (94%) of sequences carried mutations in the epitope by seven days, 36/36 (100%) by 14 days.

• NL43 was also passaged in the presence of a Nef TQGYFPDWQNY-specific CTL clone. 7/15 clones had a frameshifting or stop codon introduced by one week; F121T was also observed. The most common escape mutation for both Nef epitopes was an early stop codon at position 91.

- Several mutations selected by KEKGGLEGL-specific CTL were shown to impair the down regulation of class I MHC by Nef, in particular E93G, E93K, and a truncation mutation at position 51.
- Nef deletion mutants increased 100-fold NL-43 susceptibility to inhibition by CTL specific for epitopes in other proteins, the A2 epitopes ILKEPVHGV in RT and SLYNTVATL in p17 Gag.

**HXB2 Location** Nef (117–127)

**Author Location** Nef

**Epitope** TQGYFPDWQNY

**Epitope name** B15-TY11(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (117–127)

**Author Location** Nef (117–127 LAI)

**Epitope** TQGYFPDWQNY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**References** Culmann 1998

- Optimal peptide defined by titration.

**HXB2 Location** Nef (117–127)

**Author Location** Nef (117–127)

**Epitope** TQGYFPDWQNY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B62)

**Keywords** immunodominance

**References** Day *et al.* 2001

- No immunodominant responses were detected to four B62-restricted epitopes tested.

**HXB2 Location** Nef (117–127)

**Author Location** Nef (117–127)

**Epitope** TQGYFPDWQNY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for INF $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A\*0205/A\*0208, A30, B27, B44 but responded to HLA Bw62 epitope TQGYFPDWQNY, and one of the other individuals that was A2+, but otherwise of unknown HLA type, reacted with seven epitopes including this one.

**HXB2 Location** Nef (117–128)

**Author Location** Nef (117–128 BRU)

**Epitope** TQGYFPDWQNYT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B17, B37)

**References** Culmann *et al.* 1991

- Nef CTL clones from HIV+ donors.

**HXB2 Location** Nef (117–147)

**Author Location** Nef (117–147 LAI)

**Epitope** TQGYFPDWQNYTPGPGVRYPLTFGWICYKLVP

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide

**Species (MHC)** human

**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 1/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual.
- 10/12 tested had an IgG response to this peptide.

**HXB2 Location** Nef (118–127)

**Author Location** Nef (118–127 LAI)

**Epitope** QGYFPDWQNY

**Subtype** B

**Immunogen**

**Species (MHC)** human (B62)

**Keywords** review

**References** McMichael & Walker 1994

- Review of HIV CTL epitopes.

**HXB2 Location** Nef (118–135)

**Author Location** Nef

**Epitope** QGYFPDWQNYTPGPGRF

**Epitope name** NEF-17

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.
- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, QGYFPDWQNYTPGPgRf differs from the consensus C sequence QGYFPDWQNYTPGPvRy at 2 amino acid positions, i.e. by 11.1%.

**HXB2 Location** Nef (118–135)

**Author Location** Nef

**Epitope** QGYFPDWQNYTPGPGIRY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved

peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim et al. *J. Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.

- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, QGYFPDWQNYTPGPGIRY, had an overall frequency of recognition of 30.7% - 23.7% AA, 38.5% C, 40.9% H, 19% WI. This peptide is included in a 54 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region II', QKRQDILDWVYHTQG YFPDWQNYTPGPGIRYPLTFGWCFKLVPEPEKVEEAN, a 54 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** Nef (119–127)

**Author Location** Nef (119–127)

**Epitope** GYFPDWQNY

**Subtype** B, CRF02\_AG

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Country** Cote D'Ivoire

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons

**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 0/9 CRF02\_AG-infected Ivoirians, and 1/9 B-infected French subjects. It was invariant among 5 French subjects, including the one that reacted with the epitope, and had single amino acid substitutions in 4/8 Ivoirians.

**HXB2 Location** Nef (120–127)

**Author Location** (C consensus)

**Epitope** YFPDWQNY

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*29)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YFPDWQNY is an optimal epitope.

**HXB2 Location** Nef (120–127)

**Author Location** (C consensus)

**Epitope** YFPDWQNY

### Subtype C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*29, A\*3002)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells

**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Nef (120–127)

**Author Location**

**Epitope** YFPDWQNY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A29)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** assay standardization/improvement, epitope processing

**References** Draenert *et al.* 2004a

- 96% of optimally defined epitopes have one of only nine amino acids serving as the C-terminal anchor position. Seven amino acids are never found in this position and four are only present in 4% of cases. CD8 T-cell response to an epitope is shown to be best detected when the epitope is situated at the C-terminal end of a longer peptide, and authors suggest that Elispot reagents would be better designed if peptides ended on known C-terminal anchors.
- Instead of YFPDWQNYT, YFPDWQNY was found to be the optimal epitope in one patient.

**HXB2 Location** Nef (120–127)

**Author Location**

**Epitope** YFPDWQNY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5801, B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Feeney *et al.* 2005

- Escape mutations in TW10 and other B57-restricted epitopes were shown to arise early in infants following perinatal infection. Some escape variants were likely to have been transmitted vertically, from HLA-B57/5801 positive HIV-1 infected mothers, while others arose during infancy in cases where the children inherited the B57/5801 allele paternally. In contrast to adults, the majority of children showed a robust response to the escape variants, suggesting that infants are able to mount



functional immune responses and drive immune escape and that a developing immune system may exhibit greater plasticity in recognizing viral variants.

- YFPDWQNY responses were somewhat more frequent in adults.

**HXB2 Location** Nef (120–128)

**Author Location**

**Epitope** YFPDWQNYT

**Immunogen** HIV-1 infection

**Species (MHC)** human (A01)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope YFPDWQNYT elicited a magnitude of response of 685 SFC with a functional avidity of 5nM.

**HXB2 Location** Nef (120–128)

**Author Location** Nef (118–126 SF2)

**Epitope** YFPDWQNYT

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A1+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 0/2 group 2, and 1/2 group 3.

**HXB2 Location** Nef (120–128)

**Author Location** Nef

**Epitope** YFPDWQNYT

**Epitope name** A1-YT9(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128)

**Epitope** YFPDWQNYT

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1, B\*3701, B\*5701)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, SPRTLNAWV, was predicted to be restricted by A1, B\*3701 and B\*5701.

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128)

**Epitope** YFPDWQNYT

**Immunogen** HIV-1 infection

**Species (MHC)** human (A29)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128 LAI)

**Epitope** YFPDWQNYT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3701)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*3701 and B\*5701 epitope.

**HXB2 Location** Nef (120–128)

**Author Location**

**Epitope** YFPDWQNYT

**Epitope name** YT9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B\*57-restricted optimal epitope YFPDWQNYT was tested for immune response.

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128)

**Epitope** YFPDWQNYT

**Epitope name** YT9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CTL suppression of replication

**Keywords** class I down-regulation by Nef

**References** Adnan *et al.* 2006

- The impact of Nef on antiviral activity was studied. CTL-targeting epitopes were susceptible to the effects of Nef, both in late (Gag, RT, Env) and in early proteins (Rev, Nef), although to a lesser degree in early proteins. However, HLA-C-restricted CTLs (unlike HLA-A and HLA-B) were unaffected by Nef both in early (Nef) and late (Env) proteins.
- Early protein Nef epitope YFPDWQNYT-recognizing CTLs were less affected by Nef.

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128)

**Epitope** YFPDWQNYT

**Epitope name** nefYT9

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Country** United Kingdom, Kenya

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** TCR usage, structure, characterizing CD8+ T cells

**References** Gillespie *et al.* 2006

- CD8+ T cell repertoire recognizing KAFSPEVIPMF [KF11] and variants and the structure of individual B\*57-peptide complexes were studied.

- In addition, immunodominancy of the previously mapped B\*57 epitopes during chronic infection was assessed. KGFN-PEVIPMF and ISPRTLNAW were immunodominant both in frequency and magnitude of recognition.

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128 LAI)

**Epitope** YFPDWQNYT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*5701)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*5701 epitope.
- Subtype of B57 not determined.

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128 IIIB)

**Epitope** FFPDWKNYT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Wilson *et al.* 1999a

- This study describes maternal CTL responses in the context of mother-to-infant transmission.
- Detection of CTL escape mutants in the mother was associated with transmission, but the CTL-susceptible forms of the virus tended to be found in infected infants.
- LFPDWKNYT is an escape mutant.

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128 LAI)

**Epitope** YFPDWQNYT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B37, B57)

**References** Culmann 1998

- Nef CTL clones from HIV+ donors – optimum peptide mapped by titration.

**HXB2 Location** Nef (120–128)

**Author Location**

**Epitope** YFPDWQNYT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B37, B57)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.

- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 2 alleles previously known to be associated (B37, B57) and 5 additional alleles (A01, A02, A23, Cw02, Cw06).

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128)

**Epitope** FFPDWKNYT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 5 epitopes from this individual that varied over time where the internal mutations became fixed; a dramatic decrease in CTL activity against the wild type epitope was observed as the mutation arose. YfpdwQnyt and YfpdwHnyt variants found at 2 months postseroconversion (psc); YfpdwHnyt, YfpdwQsyt, YLpdwQsyt and YfpdwDnyt variants found 20 months psc; YfpdwDnyt and YfpdwQsyt variants found 47 months psc.

**HXB2 Location** Nef (120–128)

**Author Location**

**Epitope** YFPDWQNYT

**Epitope name** Nef-YT9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B57, 1/5 (20%) recognized this epitope.

**HXB2 Location** Nef (120–128)

**Author Location** Nef

**Epitope** YFPDWQDYT

**Epitope name** YT9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- One escape mutation, at position 7, YFPDWQnYT, was found not to correspond to the most polymorphic residue in the epitope.

**HXB2 Location** Nef (120–128)

**Author Location**

**Epitope** YFPDWQNYT

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** Nef (120–128)

**Author Location** Nef

**Epitope** YFPDWQNYT

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57, B63)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, cross-presentation by different HLA, optimal epitope

**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This epitope was recognized by 40% of B63-positive subjects and 27% of B57/58-positive subjects.

**HXB2 Location** Nef (120–128)

**Author Location**

**Epitope** YFPDWQNYT

**Immunogen**

**Species (MHC)** human (Cw6)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes that this is an Cw6 epitope.

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128)

**Epitope** YFPDWQNYT

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** immunodominance

**References** Betts *et al.* 2000

- Only 4/11 HLA-A2+ HIV+ individuals had CTL that reacted to SLYNTVATL, calling into question whether it is immunodominant.
- 95 optimally-defined peptides from this database were used to screen for IFN $\gamma$  responses to other epitopes.
- 1/11 of the A2+ individuals was HLA A\*0205/A\*0208, A30, B27, B44 but responded to HLA B37 epitope IYKRWILGL, and one of the other individuals that was A2+, but otherwise of unknown HLA type, reacted with seven epitopes including this one.

**HXB2 Location** Nef (120–128)

**Author Location** Nef (120–128)

**Epitope** YFPDWQDYT

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A3, A32, B15, B51

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimate of escape rate for this epitope, YFPDWQDYT, was found to be 0.002/day (optimistic escape rate = 0.012), with SE of 0.001.
- In the subject studied, the fluctuating outgrowth of a Q125D mutation in Nef was observed over a period of 1,361 days.

**HXB2 Location** Nef (120–144)

**Author Location** Nef (120–144 SF2)

**Epitope** YFPDWQNYTPGPGIRYPLTFGWGCK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**References** Jassoy *et al.* 1992

- Epitope recognized by CTL clone derived from CSF.

**HXB2 Location** Nef (121–128)

**Author Location** Nef (121–128)

**Epitope** FPDWQNYT

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A1)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that the vaccinated volunteers responded to.

**HXB2 Location** Nef (121–128)

**Author Location** Nef (121–128 HXB2)

**Epitope** FPDWQNYT

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Country** Viet Nam

**Assay type** HLA binding

**Keywords** subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01\_AE has 2 forms, FPDWQNYT, like the HXB2 form, and FPDWhNYT. Both are predicted to bind to A1.

**HXB2 Location** Nef (121–135)

**Author Location** Nef

**Epitope** FPDWQNYTPGPGIRY

**Epitope name** nef-5169

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, FPDWQNYTPGPGIRY was mutated in the daughter D2 isolate to FPDWQNYTPGPGtRf.

**HXB2 Location** Nef (121–135)

**Author Location** Nef (121–135)

**Epitope** FPDWQNYTPGPGIRY

**Epitope name** NY10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide has identity with the consensus peptide FPDWQNYTPGPGIRY.

**HXB2 Location** Nef (122–136)

**Author Location** Nef (122–136)

**Epitope** PDWQNYTPGPGVRYYP

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Nef (122–141)

**Author Location** Nef

**Epitope** PDWQNYTPGPGVRYPLTFGW

**Epitope name** Nef13 (containing epitope TL10)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35)

**Donor MHC** A\*02, A\*03, B\*35, B\*51

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** rate of progression, acute/early infection, memory cells

**References** Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to peptide Nef13, containing epitope TL10, TPGPGVRYPL, a patient with oscillating ART had IFN-gamma secretion by CD127 lo cells during viremia and CD127hi cell-IFN-gamma production during viremic control. Shortly after ART cessation, CD127 mixed cells secreted IFN-gamma.

**HXB2 Location** Nef (122–141)

**Author Location** Nef (121–140 SF2)

**Epitope** PDWQNYTPGPGVRYPLTFGW

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- Three of these 11 had CTL response to this peptide.
- The responding subjects were HLA-A2, B21; HLA-A3, A24, B7, B38.

**HXB2 Location** Nef (123–137)

**Author Location** Nef (123–137 IIIB)

**Epitope** QWQNYTPGPGVRYPL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** responses in children, mother-to-infant transmission, escape

**References** Wilson *et al.* 1996

- Epitope defined in the context of the Pediatric AIDS Foundation ARIEL Project, a mother-infant HIV transmission study.

- FFPDYTPGPGTRFPL and FFPDYKPGPGTRFPL, naturally occurring variants, were found in mother and are not recognized.
- LFPDYKPGPGTRFPL and FFPDYKPGPGTRFPL, naturally occurring variants, were found in infant and are not recognized.

**HXB2 Location** Nef (125–139)

**Author Location** Nef

**Epitope** QNYTPGPGIRYPLTF

**Epitope name** nef-5170

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, QNYTPGPGIRYPLTF was mutated in the daughter D2 isolate to QNYTPGPGIRfPLTF.

**HXB2 Location** Nef (125–143)

**Author Location** Nef

**Epitope** QNYTPGPGRfPLTFGWCF

**Epitope name** NEF-18

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, immunodominance

**References** Zhao *et al.* 2007

- 46 ART-naive subjects with HIV-B infection were used to study CTL cross-responses between HIV clade B and C peptide sequences. 204/826 overlapping peptide epitopes tested were common between both clades in eliciting CTL responses that were of similar magnitude and frequency in both HIV-B

and -C. Higher magnitudes and frequencies of responses were detected with peptides from Gag, Pol, Env and Nef proteins, while peptides from Rev, Vif, Vpu, Vpr and Tat were recognized less often.

- 27 peptides from immunodominant regions of higher inter-clade homology in Gag, Nef, Pol, Vpr, Env and Vif were found to be common between both clades in eliciting the greatest CTL responses. Although these 27 peptides differed by up to 39% between clades, CTL responsiveness was not affected.
- Cross-recognized peptides had a lower entropy of recognition than clade-B specific variants, suggesting that published conserved clade-B sequences are also more conserved between clades. Consensus sequences therefore occurred in virus regions of low intra-clade entropy and high inter-clade homology.
- 18/27 highly immunogenic clusters were previously reported by Frahm *et al.* [J. Virol. 78:2187-2200 (2004)].
- This peptide, QNYTPGPGRfPLTFGWCF differs from the consensus C sequence QNYTPGPGvRyPLTFGWCF at 2 amino acid positions, i.e. by 10.5%.

**HXB2 Location** Nef (126–135)

**Author Location** Nef (126–135 BRU)

**Epitope** NYTPGPGVRY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Keywords** binding affinity, epitope processing

**References** Chopin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- NYTPGPGVRY was recognized in 3/10 (30%) of individuals with HLA A24. It was a moderate affinity HLA-A24 binder.

**HXB2 Location** Nef (126–138)

**Author Location** Nef (126–138 BRU)

**Epitope** NYTPGPGVRYPLT

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Culmann *et al.* 1991

- Nef CTL clones from HIV+ donors.

**HXB2 Location** Nef (126–140)

**Author Location** Nef (126–140)

**Epitope** NYTPGPGTRYPLTFG

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, NYTPGPGtRYPLTFG, varies at position 8 (threonine) from the consensus peptide QNYTPGPGIRYPLTF.

**HXB2 Location** Nef (126–140)

**Author Location** Nef (126–140)

**Epitope** NYTPGPGtRYPLTFG

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope, NYTPGPGtRYPLTFG, varies from the consensus peptide at position 8.

**HXB2 Location** Nef (126–140)

**Author Location** Nef (126–140)

**Epitope** NYTPGPGtRYPLTFG

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A23, B62

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- NYTPGPGtRYPLTFG is a previously unpublished epitope, varying from the consensus at position 8 (threonine).

**HXB2 Location** Nef (126–143)

**Author Location** Nef

**Epitope** NYTPGPGIRYPLTFGWCF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Barbados, Haiti, United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** binding affinity, immunodominance

**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J.Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, NYTPGPGIRYPLTFGWCF, had an overall frequency of recognition of 37.3% - 42.4% AA, 38.5% C, 31.8% H, 33.3% WI. This peptide is included in a 54 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region II', QKRQDILDWVYHTQGYFPDWQNYTPGPGIRYPLTFGWCFKLVPEPEKVEEAN, a 54 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** Nef (127–135)**Author Location** Nef (126–)**Epitope** YTPGPGVRY**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A1)**Country** India**Assay type** Other**Keywords** subtype comparisons**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope YTPGPGVRY, is predicted to bind HLA-A1 with a binding affinity score of 2.5.

**HXB2 Location** Nef (127–135)**Author Location****Epitope** YTPGPGIRY**Immunogen****Species (MHC)** human (B57)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes that this is an B57 epitope.

**HXB2 Location** Nef (127–135)**Author Location** Nef**Epitope** YTPGPGIRY**Epitope name** YY9**Subtype** B, C**Immunogen** HIV-1 infection**Species (MHC)** human (B57, B58)**Donor MHC** A02, A33, B35, B57, Cw04, Cw07**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** cross-presentation by different HLA, optimal epitope**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- This is a putative HLA-B63/57/58 epitope containing the B58 supertype binding motif. The optimal epitope was defined in a person carrying B57, and reactivity to the peptide was enriched in those with B57/B58, just a trend for B63.

**HXB2 Location** Nef (127–135)**Author Location****Epitope** YTPGPGIRY**Immunogen****Species (MHC)** human (B63)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes that this is an B63 epitope.

**HXB2 Location** Nef (127–141)**Author Location** Nef (127–141)**Epitope** YTPGPGVRYPLTFGW**Epitope name** RW8**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A24)**Donor MHC** A24, A3, B7**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** computational epitope prediction, vaccine-induced epitopes**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, YTPGPGvRYPLTFGW, varies at position 7 (valine) from the consensus peptide PGPGIRYPLTFGWCF.

**HXB2 Location** Nef (127–141)**Author Location** Nef (127–141)**Epitope** YTPGPGVRYPLTFGW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** subtype comparisons**References** Novitsky *et al.* 2002

- HLA, viral sequence, and Elispot data was obtained from 105 HIV-1 positive Botswanans; Elispot data was obtained from between 55 and 64 subjects for each HIV protein.
- Nef and p24 had the highest percentage of reactive peptides, and p24 had the highest magnitude of HIV-1 responses.
- This peptide was among the 8 most reactive C clade peptides from among over 350 tested spanning all HIV proteins.

**HXB2 Location** Nef (128–135)**Author Location** Nef (128–135 LAI)**Epitope** TPGPGVRY**Subtype** B**Immunogen** in vitro stimulation or selection**Species (MHC)** human (B\*0702)**Keywords** epitope processing**References** Lucchiari-Hartz *et al.* 2000

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152.
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments.



- Both TPGPGVRYPL and TPGPGVRY are naturally processed ligands that can be eluted from HLA-B7 molecules, both are recognized by the same CTL, and both peptides seem to be the direct product of a proteasomal digest.
- The peptide TPGPGVRY is present in a high copy number, TPGPGVRYPL at a more moderate level, possibly due to a major cleavage site between the Y and P.

**HXB2 Location** Nef (128–135)

**Author Location** Nef (128–135)

**Epitope** TPGPGVRY

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (B7 supertype)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** Nef (128–136)

**Author Location** Nef (128–136)

**Epitope** TPGPGVRYPL

**Epitope name** TP9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*07)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** rate of progression, acute/early infection, memory cells

**References** Sabbaj *et al.* 2007

- CD127 hi memory CTLs were correlated with different patient groups - subjects with chronic HIV-1 infection or controllers or those treated early with ART. For patients with chronic infection, CD127 hi CTL levels decrease greatly. Early ART treatment alone maintained these long-lived memory T cells.
- In response to epitope TP9, TPGPGVRYPL, IFN-gamma was produced by CD127 mix cells in patients with chronic infection and viremia. Chronically infected patients with low VL did not secrete IFN-gamma.

**HXB2 Location** Nef (128–136)

**Author Location**

**Epitope** TPGPGVRYPL

**Epitope name** Nef-TP9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA B07, 4/9 (44%) recognized this epitope.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137 LAI)

**Epitope** TPGPGVRYPL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*0702 epitope.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137 LAI)

**Epitope** TPGPGVRYPL

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (B\*0702)

**Keywords** epitope processing

**References** Lucchiari-Hartz *et al.* 2000

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152.
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments.
- Both TPGPGVRYPL and TPGPGVRY are naturally processed ligands that can be eluted from HLA-B7 molecules, both are recognized by the same CTL, and both peptides seem to be the direct product of a proteasomal digest.
- The peptide TPGPGVRY is present in a high copy number, TPGPGVRYPL at a more moderate level, possibly due to a major cleavage site between the Y and P.

**HXB2 Location** Nef (128–137)

**Author Location** (C consensus)

**Epitope** TPGPGVRYPL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*0702)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- TPGPGVRYPL is an optimal epitope for B\*4201 and B\*0702.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137)

**Epitope** TPGPGVRYPL

**Epitope name** TL10

**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702, B\*4201)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, Other  
**Keywords** supertype, cross-presentation by different HLA, TCR usage, HLA associated polymorphism  
**References** Leslie *et al.* 2006

- 14 promiscuous HIV-specific CTL epitopes presented by B7 supertype alleles were described. It was shown that CTLs targeting an identical epitope that are restricted by closely related but different HLA alleles differ in several ways: by occurrence of distinct HLA-specific escape mutations, by recruitment of distinct TCRs by peptide/MHC complexes, and by functional avidity of CTLs. Since there were no differences in the frequency, magnitude or immunodominance of the CTL responses restricted by different HLA alleles, it is suggested that the unique peptide/MHC complexes generated by closely related HLA induce qualitatively different CTL responses.
- Functional avidity is correlated with selection pressure observed in HLA allele-epitope restriction
- Only B\*0702 was found to be associated with polymorphism.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137)

**Epitope** TPGPGTRYPL

**Epitope name** TL10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 2 PTE-B peptide sequences were identified, NYTPGPGtRY-PLTFG and YTPGPGvRYPLTFGW, containing variants of this consensus epitope sequence TL10, viz. TPGPGtRYPL and TPGPGvRYPL, both of which elicited a IFN-gamma immune response.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (127–136)

**Epitope** TPGPGVRYPL

**Epitope name** TL10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*3501)

**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** escape, acute/early infection

**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.
- Point mutation at position 2 (P to S, TsGPGVRYPL) was detected at a chronic infection time point, month 33. This escape variant had lower avidity.
- The response to the peptide that carried this epitope was initially strong and diminished over time.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137 LAI)

**Epitope** TPGPGVRYPL

**Subtype** B

**Immunogen**

**Species (MHC)** human (B\*4201)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*4201 epitope.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137)

**Epitope** TPGPGVRYPL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201)

**Donor MHC** A\*30, A\*3001, B\*1503, B\*4201, Cw\*0202, Cw\*1701; A\*0301, A\*3001, B\*4201, B\*5802, Cw\*0602, Cw\*1701

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection

**References** Pillay *et al.* 2005

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- Escape variants tSgpgvrypl and tQgpgvrypl were rapidly selected in an infant, by 26 weeks, but were not found in the infant's mother. These forms were demonstrated to be escape mutations by Elispot, and also had reduced binding to B\*4201 in a competitive inhibition assay.

**HXB2 Location** Nef (128–137)

**Author Location** (C consensus)

**Epitope** TPGPGVRYPL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*4201)

**Country** South Africa

- Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007
- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
  - TPGPGVRYPL is an optimal epitope for B\*4201 and B\*0702.
- HXB2 Location** Nef (128–137)  
**Author Location**  
**Epitope** TPGPGVRYPL  
**Epitope name** TL10  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*4201)  
**Country** South Africa  
**Assay type** proliferation, Tetramer binding, Intracellular cytokine staining  
**References** Day *et al.* 2006
  - PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

**HXB2 Location** Nef (128–137)  
**Author Location** (C consensus)  
**Epitope** TPGPGVRYPL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*0702, B\*4201)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells  
**References** Kiepiela *et al.* 2004
  - HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
  - This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Nef (128–137)  
**Author Location**  
**Epitope** TPGPGVRYPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B07)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, immunodominance, optimal epitope  
**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
  - The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
  - EBV response patterns were not significantly altered by HIV coinfection.
  - Epitope TPGPGVRYPL elicited a magnitude of response of 210 SFC with a functional avidity of 0.5nM and binding affinity of 5.1nM.
- HXB2 Location** Nef (128–137)  
**Author Location** Nef (128–137 BRU)  
**Epitope** TPGPGVRYPL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Keywords** binding affinity, epitope processing  
**References** Chopin *et al.* 2001
  - Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
  - 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
  - TPGPGVRYPL was recognized in 8/16 (50%) of individuals with HLA B7, and 1/9 (11%) of individuals with HLA B35. It was a high affinity HLA binder.

**HXB2 Location** Nef (128–137)  
**Author Location**  
**Epitope** TPGPGVRYPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Keywords** acute/early infection  
**References** Wilson *et al.* 2000a
  - Three individuals with highly focused HIV-specific CTL responses were studied during acute infection using tetramers – high frequencies of HIV-1-specific CD8+ T cells were found prior to seroconversion, and there was a close temporal relationship between the number of circulating HIV-specific T cells and viral load was also found.
  - All three patients were B\*2705, with HLA alleles: A1, A30/31, B\*2705, B35; A1, A\*0301, B7, B\*2705; and A\*0201, A\*0301, B\*2705, B39.
  - ELISPOT was used to test a panel of CTL epitopes that had been defined earlier and were appropriate for the HLA haplotypes of the study subjects – 3/3 subjects showed a dominant response to the B\*2705 epitope KRWILGGLNK.
  - The subject with A\*0201 had a moderately strong response to SLYNTVATL.

- Weak responses were observed to A\*301-RLRPGGKKK, A\*301-QVPLRPMTYK, and B7-TPGPGVRYPL in the subject who was HLA A1, A\*0301, B7, B\*2705.
- No acute response was detected to the following epitopes: A\*201-ILKEPVHGV, A\*301-KIRLRPGGK, A\*301-AIFQSSMTK, A\*301-TVYYGVPVWK, B35-EPIVGAETF, B35-HPDIVIYQY, B35-PPIPVGEIY, B35-NSSKVSQNY, B35-VPLRPMTY, B35-DPNPQEVVL.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137 LAI)

**Epitope** TPGPGVRYPL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Haas *et al.* 1996; Haas *et al.* 1997

- There was a high degree of variation in three CTL epitopes in Nef in four slow and non-progressors, and variant specific CTLs arose over time to eliminate variants, indicating immune selection.
- The epitope position was taken from Haas *et al.* [1997]

**HXB2 Location** Nef (128–137)

**Author Location** Nef

**Epitope** TPGPGVRYPL

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B7)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The D subtype consensus is identical to the B clade epitope.
- The A subtype consensus is TPGPGIRYPL.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (subtype B)

**Epitope** TPGPGVRYPL

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B7)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among B and D clade viruses.
- The Clade A version of the epitope: TPGPGIRYPL.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137)

**Epitope** TPGPGVRYPL

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (B7)

**Keywords** immunodominance, dendritic cells, Th1

**References** Wilson *et al.* 1999b

- Dendritic cells are the most potent for priming T cell responses – DCs can stimulate autologous CTL responses from T cells cultured from HIV negative donors.
- Th1-biasing cytokines IL-12 or IFN alpha enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within.
- CTL from a B7 donor displayed no reactivity to this epitope, although it had been immunodominant in another study Haas *et al.* [1996]

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137 SF2)

**Epitope** TPGPGVRYPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B7+ individuals that had a CTL response to this epitope broken down by group: 0/4 group 1, 0/3 group 2, and 1/1 group 3.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137)

**Epitope** TPGPGVRYPL

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B7)

**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.

- Among HLA-B7 women, 4/5 HEPS and 5/6 HIV-1 infected women recognized this epitope.
- The dominant response to this HLA allele was to this epitope in 3 of the 4/5 HEPS cases and in 2 of the 5/6 HIV-1 infected women.
- Subject ML 1203 started with CTL responses to A\*6802 DTVLEDINL and to B7 FVPVTPQVPLR prior to seroconversion, and upon seroconversion acquired additional responses to A\*6802 ETAYFILKL which became dominant, B7 TPGPG(V/I)RYPL, B7 IPRRIRQGL, and B7 SPRTLNAWV.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137)

**Epitope** TPGPGVRYPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**References** Appay *et al.* 2000

- Combined tetramer and intracellular cytokine staining was used to study the function of circulating CD8+ T cells specific for HIV and CMV.
- HIV-specific CD8+ T cells expressed lower levels of perforin than CMV-specific CD8+ T cells from the same donor, and this was associated with persistent CD27 expression on HIV-specific cells, suggesting impaired maturation.
- In most donors, between 50% and 95% of the activated virus-specific CD8+ T cells produced IFN- $\gamma$  and MIP-1 $\beta$  with a distinct subset that failed to produce TNF- $\alpha$ .

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137)

**Epitope** TPGPGVRYPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.
- Subjects with chronic HIV-1 infection recognized between 2-8 out of 11 B7-restricted epitopes.
- An acute seroconverter homozygous for the B7 allele recognized five B7-restricted epitopes.
- The other acute seroconverter failed to recognize any of the 11 B7-restricted epitopes tested.
- The B7-restricted CTL response was highly variable and there was no clearly dominant epitope.

**HXB2 Location** Nef (128–137)

**Author Location** Nef (128–137 BRU)

**Epitope** TPGPGVRYPL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Keywords** binding affinity, epitope processing

**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- TPGPGVRYPL was recognized in 8/16 (50%) of individuals with HLA B7, and 1/9 (11%) of individuals with HLA B35. It was a high affinity HLA binder.

**HXB2 Location** Nef (128–137)

**Author Location** Nef

**Epitope** TPGPGVRYPL

**Epitope name** B7-TL10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A3, B7, Cw7

**Keywords** dynamics, supervised treatment interruptions (STI), acute/early infection

**References** Yu *et al.* 2002a

- CTL responses in 18 acutely HIV-infected HLA-A3 (n=7) or -B7 (n=4) or both -A3 and B7 (n=7) positive individuals were studied.
- One individual, AC-06, was homozygous at all three class I alleles (A3, B7, Cw7), was treated during acute infection and had supervised treatment interruptions (STI). He had only two detectable CTL responses during acute infection, but after STI this broadened to 27 distinct epitopes including 15 restricted by HLA-A3, 11 by HLA-B7, and 1 by HLA-Cw7.
- 0/11 HLA-B7 individuals had detectable B7-restricted responses to this epitope during acute infection – 10/15 of HLA-B7 epitopes tested were targeted by at least one person during acute infection. 2/4 individuals had detectable responses to this epitope after STI.

**HXB2 Location** Nef (128–137)

**Author Location** Nef

**Epitope** TPGPGVRYPL

**Immunogen** HIV-1 infection

**Species (MHC)** human (B7)

**Donor MHC** A2, A3, B7, Bw6

**Keywords** HAART, ART

**References** Appay *et al.* 2002

- Four HIV patients with prolonged clinically successful anti-viral therapy but with ongoing evidence of replication and Nef mRNA transcription, showed specific T-cell responses by Elispot and Tetramer staining, maintained for 2-4 years after initiation of HAART.
- Nef epitope recognition was detected in all 4 subjects, gp120, Pol and Gag-specific in 1 or 2 subjects.
- The HIV-specific CD8+ T-cells had an intermediate maturation phenotype characterized by low levels of perforin and high levels of CD27 expression.

- HXB2 Location** Nef (128–137)  
**Author Location** Nef  
**Epitope** TPGPGVRYPL  
**Subtype** B, C  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade  
*HIV component:* p17 Gag, p24 Gag  
**Species (MHC)** human, macaque (B7)  
**Keywords** subtype comparisons, epitope processing, vaccine-specific epitope characteristics, immunodominance  
**References** Hanke & McMichael 2000; Wee *et al.* 2002
- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polyepitope string of conserved, often immunodominant epitopes that were selected to have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].
  - Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  ELISPOT assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

- HXB2 Location** Nef (128–137)  
**Author Location** Nef  
**Epitope** TPGPGVRYPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Country** Netherlands  
**Assay type** CD8 T-cell ELISPOT - IFN $\gamma$   
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Koning *et al.* 2004
- A high-risk seronegative group of 29 homosexual men showed reduced cellular in vitro susceptibility for HIV infection and enhanced production of RANTES compared to 15 men who went on to seroconvert. Significantly higher frequencies of HLA A\*11, A\*31 and Cw\*15 were also found in the high risk seronegative men. Both groups of men had low frequencies of HIV-1 specific CD8+ T-cells, which may signify exposure more than protection from infection.
  - No one, 0/9 HLA B7+ infection-resistant men, and 0/4 pre-seroconversion men who went on to become infected, reacted to this epitope.

- HXB2 Location** Nef (128–137)  
**Author Location** Nef (126–135)  
**Epitope** TPGPGVRYPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)

- Country** Spain  
**Assay type** proliferation, CD8 T-cell ELISPOT - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction  
**References** Plana *et al.* 2004
- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
  - 6/7 patients recognized this epitope, it was the most commonly recognized of 11 B\*07 epitopes.

- HXB2 Location** Nef (128–137)  
**Author Location** (B consensus)  
**Epitope** TPGPGVRYPL  
**Epitope name** TL10  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Donor MHC** A31, A68, B07, B70, Cw1, Cw7  
**Country** United States  
**Assay type** Cytokine production, Intracellular cytokine staining, Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** assay standardization/improvement, memory cells, characterizing CD8+ T cells  
**References** Lichterfeld *et al.* 2004c
- Using a flow-cytometric cytotoxicity assay based on caspase-3 activation in dying target cells, it was shown that the subset of HIV-1-specific CD8+ T cells secreting both IFN-gamma and TNF-alpha exhibit stronger cytotoxic activity than those secreting only IFN-gamma. These cells also exhibited stronger intracellular perforin expression. No association between HIV-1-specific CD8+ T-cell maturation phenotypes and intracellular perforin expression was found.
  - 1/9 individuals recognized this epitope.

- HXB2 Location** Nef (128–137)  
**Author Location** Nef  
**Epitope** TPGPGVRYPL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Country** United Kingdom  
**Assay type** Tetramer binding, T-cell ELISPOT, Intracellular cytokine staining  
**Keywords** rate of progression, acute/early infection, characterizing CD8+ T cells, immune dysfunction  
**References** Papagno *et al.* 2004
- Acute HIV-1 infection induces massive activation of HIV-specific and non-HIV-specific CD8+ T-cells resulting in differentiation of these cells. High differentiation of CD8+ T-cells is correlated with disease progression. Differentiation is a natural process but it can be driven by elevated immune activation, such as in HIV infection.

**HXB2 Location** Nef (128–137)  
**Author Location** Nef (128–137)  
**Epitope** TPGPGVRYPL  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21  
**Species (MHC)** human (B7 supertype)  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization  
**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+ T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** Nef (128–137)  
**Author Location** Nef (128–137 subtype B)  
**Epitope** TPGPGVRYPL  
**Subtype** B  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (B\*8101, B7)  
**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNT-VATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** Nef (128–137)  
**Author Location** Nef (subtype B)  
**Epitope** TPGPGVRYPL  
**Subtype** B  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (B\*8101, B7)  
**Keywords** subtype comparisons  
**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- Clade A version of the epitope: TPGPGIRYPL, clade D version: TPGPGIRYPL.

**HXB2 Location** Nef (128–137)  
**Author Location** Nef  
**Epitope** TPGPGIRYPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was recognized by 1/22 HEPS control sex workers, ML851.

**HXB2 Location** Nef (129–143)  
**Author Location** Nef  
**Epitope** PGPGRYPLTFGWCF  
**Epitope name** nef-5171  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)  
**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism  
**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, PGPGRYPLTFGWCF was mutated in the daughter D2 isolate to PGPGRfRfPLTFGWCF.

**HXB2 Location** Nef (129–143)  
**Author Location** Nef (129–143)  
**Epitope** PGPGRfRfPLTFGWCF

**Epitope name** RW8**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A23)**Donor MHC** A23, B62**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** computational epitope prediction, vaccine-induced epitopes**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, PGPGtRfPLTFGWCF, varies at positions 5 and 7 from the consensus peptide PGPGIRYPLTFGWCF.

**HXB2 Location** Nef (129–143)**Author Location** Nef (129–143)**Epitope** PGPGTRFPLTFGWCF**Subtype** B**Immunogen** computer prediction, HIV-1 and GBV-C coinfection**Species (MHC)** human (A24)**Donor MHC** A24, A3, B7**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** computational epitope prediction, vaccine-induced epitopes**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, PGPGtRfPLTFGWCF, varies at positions 5 (threonine) and 7 (phenylalanine) from the consensus PCP-CIRYPLTFGWCF.

**HXB2 Location** Nef (129–143)**Author Location** Nef (129–143)**Epitope** PGPGTRFPLTFGWCF**Epitope name** YF9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Donor MHC** B\*1503, B35, B7 supertype, Cw7**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** computational epitope prediction, vaccine-induced epitopes**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide PGPGtRfPLTFGWCF varies at positions 5 and 7 from the consensus peptide PGPGIRYPLTFGWCF.

**HXB2 Location** Nef (129–143)**Author Location** Nef (129–143)**Epitope** PGPGIRYPLCFGWCF**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Donor MHC** B\*1503, B35, B7 supertype, Cw7**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** computational epitope prediction, vaccine-induced epitopes**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide PGPGIRYPLcFGWCF varies at position 10 from the consensus peptide IRYPLTFGWCFKLVP.

**HXB2 Location** Nef (130–139)**Author Location** Nef (130–139 BRU)**Epitope** GPGVRYPLTF**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B35)**Keywords** binding affinity, epitope processing**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.



- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- GPGVRYPLTF was recognized in 0/10 (0%) of individuals with HLA B7, and 1/11 (9%) of individuals with HLA B35, although it was a high affinity HLA binder.

**HXB2 Location** Nef (130–143)

**Author Location** Nef (130–143 LAI)

**Epitope** GPGVRYPLTFGWCY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**References** Goulder *et al.* 1996b

- CTL response to this epitope observed in 4 long-term survivors.
- Peptide defined on the basis of B\*5801 binding motif, yet not cross-restricted except at high concentrations.

**HXB2 Location** Nef (130–143)

**Author Location**

**Epitope** GPGIRYPLTFGWCF

**Epitope name** GF14

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*57)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Bailey *et al.* 2006b

- Impact of CTL escape mutations in HLA-B57 positive elite suppressors was examined. Escape mutations in B57-restricted Gag epitopes were present in all viruses derived from plasma but were lacking in proviruses, suggesting a strong selective pressure acting upon virus in plasma. IFN-gamma responses were detected to both wild-type epitopes and mutant plasma virus epitopes. In some individuals, CD8 IL-2 secretion, rather than IFN-gamma responses, showed better correlation with the plasma viral variants.
- HLA-B\*57-restricted peptide GPGIRYPLTFGWCF was tested for immune response.

**HXB2 Location** Nef (130–143)

**Author Location** Nef (121–141)

**Epitope** GPGVRYPLTFGWCY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**References** Ferrari *et al.* 2000

- One of the 51 HIV-1 epitopes selected by Ferrari *et al.* as good candidate CTL epitopes for vaccines by virtue of being conserved and presented by common HLA alleles.

**HXB2 Location** Nef (130–143)

**Author Location** Nef (128–141)

**Epitope** GPGVRYPLTFGWCY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B57)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 7/7 patients recognized this epitope.

**HXB2 Location** Nef (130–144)

**Author Location** Nef (130–144 HXB2)

**Epitope** GPGVRYPLTFGWCYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** T-cell Elispot

**Keywords** supervised treatment interruptions (STI), immunodominance, early treatment

**References** Addo *et al.* 2003

- Comprehensive Elispot screening of 504 overlapping peptides that spanned all HIV-1 proteins in 57 HIV-1 infected individuals. Four groups of patients were compared: 23 were untreated; 12 patients were chronically infected and treated; 22 started treatment during acute infection, 11 continuously treated and 11 with STI.
- 63% of the peptides were recognized - the most frequent responses were directed against Nef (95%) and p24-Gag (88%). p17 was the most frequently recognized protein after correction for protein length. A median of 18 peptides (range 2-42) were recognized per person. The most frequently (>20%) recognized peptides were located in conserved regions within clade B sequences. Vpu was rarely recognized.
- A decrease in the total magnitude and in the breadth of CTL responses was detected in patients with treated acute infection in comparison to chronically infected treated or untreated individuals. No correlation between plasma viral load and HIV-1 specific T-cell responses was observed.
- The authors did not note the reference strain, but based on the peptide sequences provided it appears to be HXB2.
- Responses to this peptide were detected in 24% of the study subjects, and it was one of the 25 most frequently recognized peptides.

**HXB2 Location** Nef (131–145)

**Author Location** Nef (131–145)

**Epitope** PGIRYPLTFGWCFKL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A23)

**Donor MHC** A23, B62

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, PGIRYPLTFGWCFKL, has identity with the consensus peptide IRYPLTFGWCFKLVP from positions 133-145.

**HXB2 Location** Nef (131–145)

**Author Location** Nef (131–145)

**Epitope** PGIRYPLTFGWCFKL

**Subtype** B

**Immunogen** computer prediction, HIV-1 and GBV-C co-infection

**Species (MHC)** human (A24)

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, PGIRYPLTFGWCFKL, is a variant of the consensus peptide IRYPLTFGWCFKLVP.

**HXB2 Location** Nef (131–145)

**Author Location** Nef (131–145)

**Epitope** PGIRYPLTFGWCFKL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing

Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.

- This epitope, PGIRYPLTFGWCFKL, has identity with the consensus peptide IRYPLTFGWCFKLVP from positions 133-145.

**HXB2 Location** Nef (132–144)

**Author Location** Nef

**Epitope** GIRYPLTFGWCFK

**Immunogen**

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Jubier-Maurin *et al.* 1999

- 41 new HIV-1 strains describing envelope subtypes of HIV-1 A-H were genetically characterized in the nef region – 34 subtypes were classified in the same subtype in nef and env and 7 of the 41 strains were recombinants.
- This region was defined as a CTL epitope region that is conserved among HIV-1 M group subtypes.

**HXB2 Location** Nef (132–146)

**Author Location** Nef (132–146)

**Epitope** GVRYPPLTLGWCFKLV

**Subtype** B

**Immunogen** computer prediction, HIV-1 and GBV-C co-infection

**Species (MHC)** human (A24)

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, GvRYPLTIGWCFKLV, varies at positions 2 (valine) and 8 (leucine) from the consensus peptide IRYPLTFGWCFKLVP.

**HXB2 Location** Nef (132–147)

**Author Location** Nef (132–147 BRU)

**Epitope** GVRYPPLTFGWCFKLV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1, B8)

**References** Hadida *et al.* 1992

- HIV-1 specific CTLs detected in lymphoid organs.

**HXB2 Location** Nef (132–147)

**Author Location** Nef (132–147 BRU)  
**Epitope** GVRYPPLTFGWYKLVLP  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B18)  
**References** Culmann *et al.* 1991  
 • Nef CTL clones from HIV+ donors.

**HXB2 Location** Nef (132–147)  
**Author Location** Nef (132–147)  
**Epitope** GVRYPPLTFGWYKLVLP  
**Immunogen** vaccine  
*Vector/Type:* DNA, DNA with protein boost  
*Strain:* B clade LAI *HIV component:* Gag, Nef, Tat *Adjuvant:* IL-18  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**Keywords** Th1  
**References** Billaut-Mulot *et al.* 2001  
 • DNA vaccinated BALB/c mice primed and boosted with the multiepitopic vaccine with IL18 showed lymphoproliferative responses 7 weeks post immunization.  
 • Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime/DNA boost was more effective than DNA prime protein boost.  
 • Immunization with either the multiepitopic DNA or with the mixed DNA vaccine induced HIV-1 specific Th1 cytokines (IL-2 and IFN- $\gamma$ )  
 • Co-administration of IL18 increased T-cell responses but decreased anti-HIV antibody levels.

**HXB2 Location** Nef (133–141)  
**Author Location** Nef (133–141)  
**Epitope** TRYPLTFGW  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A33)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Nef (133–141)  
**Author Location** Nef (132–)  
**Epitope** VRYPLTFGW  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*2702, B\*2705)  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons  
**References** Kumar *et al.* 2006a  
 • Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.  
 • Of the most common HLA in India tested, this epitope VRYPLTFGW, is predicted to bind HLAs - B\*2702 and B\*2705 with binding affinity scores of 500 and 1000.

**HXB2 Location** Nef (133–147)  
**Author Location** Nef (133–147)  
**Epitope** TRYPLTFGWYKLVLP  
**Subtype** B

**Immunogen** computer prediction, HIV-1 and GBV-C co-infection  
**Species (MHC)** human (A24)  
**Donor MHC** A24, A3, B7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** computational epitope prediction, vaccine-induced epitopes  
**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide TRYPLTFGWYKLVLP is a variant of the consensus peptide IRYPLTFGWCFKLVLP and it varies at the 11th position.

**HXB2 Location** Nef (133–147)  
**Author Location** Nef (133–147)  
**Epitope** TRYPLTFGWYKLVLP  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Donor MHC** B\*1503, B35, B7 supertype, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** computational epitope prediction, vaccine-induced epitopes  
**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide, TRYPLTFGWYKLVLP, varies at position 11 from the consensus peptide IRYPLTFGWCFKLVLP.

**HXB2 Location** Nef (133–148)  
**Author Location** Nef (133–148 LAI)  
**Epitope** VRYPLTFGWYKLVLP  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (B57)  
**References** Brander & Walker 1996

- P. Goulder, pers. comm.

**HXB2 Location** Nef (134–141)

**Author Location** (C consensus)**Epitope** RYPLTFGW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2301)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** characterizing CD8+ T cells**References** Kiepiela *et al.* 2004

- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.
- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Nef (134–141)**Author Location** (C consensus)**Epitope** RYPLTFGW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2301)**Country** South Africa**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** epitope processing, rate of progression, optimal epitope**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- Mutational patterns in a residue outside of the optimized epitope of RYPLTFGW are associated with the presence of the HLA presenting molecule in the host.

**HXB2 Location** Nef (134–141)**Author Location** Nef (138–147 LAI)**Epitope** RYPLTFGW**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2402)**Keywords** optimal epitope**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*2402 epitope.

**HXB2 Location** Nef (134–141)**Author Location** Nef (169–176)**Epitope** RYPLTFGW**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2402)**Assay type** Other**Keywords** HLA associated polymorphism**References** Boutwell & Essex 2007

- All HIV-1 subtype C protein sequences were analyzed, and 94 HLA-associated amino acid polymorphisms were found that were well distributed throughout the proteome. These sequences were compiled from publicly available databases and originated in South Africa and Botswana. Many polymorphisms were associated with multiple HLA allele classes. 12% of negative associations were found as well, where there was an association of virus expression of the consensus amino acid with a specific HLA allele. HLA-B alleles were involved in most of the associations. 19 HLA-associated polymorphisms were embedded in previously defined epitopes presented by an appropriate HLA restricting molecule.
- RYPLTFGW was a previously defined A\*2402 presented epitope that encompassed an A\*24 associated polymorphism, RYPLTFGW, in the second position.

**HXB2 Location** Nef (134–141)**Author Location** Nef**Epitope** RYPLTFGW**Immunogen** peptide-HLA interaction**Species (MHC)** human (A\*2402)**Assay type** Tetramer binding**Keywords** binding affinity**References** Gillespie *et al.* 2007

- MHC can exert a protective effect on HIV-1 disease progression by the interaction of MHC Class I molecules with Killer Inhibitory Receptors (KIR) of the innate immune system. Here, KIR3DS1, a putative stimulatory receptor and allele of the inhibitory KIR3DL1, is studied. Bw4 MHC Class I proteins were implicated in this KIR's ligand specificity, but the authors were unable to generate binding of Bw4Ile80 tetramers in complex with epitopes to KIR3DS1 transiently expressed on 293-T cells, using a panel of HIV-epitopes differing at p7 and p8.
- This epitope, RYPLTFGW (MHC Class I restriction, serotype Bw4) complexed with MHC A\*2402 as a tetramer was unable to bind KIR3DS1 at 4, 20 and 37C. However, the A\*2402-KYKLLKHIVW complex does bind inhibitory KIR3DL1 subtype KIR3DL1\*005.

**HXB2 Location** Nef (134–141)**Author Location** Nef (138–147 SF2)**Epitope** RYPLTFGW**Immunogen** HIV-1 infection**Species (MHC)** human (A24)**Keywords** HAART, ART, acute/early infection**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.

- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A24+ individuals that had a CTL response to this epitope broken down by group: 0/0 group 1, 2/3 group 2, and 0/0 group 3.

**HXB2 Location** Nef (134–141)

**Author Location** Nef

**Epitope** RYPLTFGW

**Epitope name** A24-RW8(Nef)

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A24, B27, B7

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Altfield *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.
- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient C displayed the greatest response to B27-KK10(p24), and in decreasing order also responded to A24-RW8(Nef), B7-IL9(gp41), A24-RL9(gp41), A24-YL8(gp41), and B7-TM9(Nef).

**HXB2 Location** Nef (134–141)

**Author Location** Nef

**Epitope** RYPLTFGW

**Epitope name** A24-WR8(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.

- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (134–141)

**Author Location**

**Epitope** RYPLTFGW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.
- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope KTKPPLPSVKK elicited a magnitude of response of 252 SFC with a functional avidity of 0.001nM.

**HXB2 Location** Nef (134–141)

**Author Location**

**Epitope** RYPLTFGW

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** supertype, cross-presentation by different HLA

**References** Frahm *et al.* 2007

- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
- Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 1 allele previously known to be associated (A24) and 5 additional alleles (A01, A02, A23, Cw04, Cw07).

**HXB2 Location** Nef (134–141)

**Author Location** Nef (134–141)

**Epitope** RYPLTFGW

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (A33)**Donor MHC** A3, A33, B14, B35, Cw\*0401, Cw\*0802**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** binding affinity, acute/early infection, early-expressed proteins**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** Nef (134–141)**Author Location** Nef (134–141 LAI)**Epitope** RYPLTFGW**Subtype** B**Immunogen****Species (MHC)** human (B27)**References** Culmann 1998

- Optimal peptide defined by titration.

**HXB2 Location** Nef (134–143)**Author Location** Nef (134–143)**Epitope** RYPLTFGWCF**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*24)**Donor MHC** A\*03, A\*24, B\*35, B\*40**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** acute/early infection, variant cross-recognition or cross-neutralization, superinfection, characterizing CD8+ T cells**References** Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting

to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.

- The response to the peptide that carried this epitope, RYPLTFGWCF, was present before superinfection but waned afterward. The epitope from the second strain had a mutation, rypICfgwcf. A second overlapping epitope in the reactive peptide might be involved, the B\*35 epitope YPLTFGWCF.

**HXB2 Location** Nef (134–143)**Author Location** Nef (138–147 SF2)**Epitope** RYPLTFGWCF**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2402)**References** Ikeda-Moore *et al.* 1997

- Defined using reverse immunogenetics – 59 HLA-A\*2402 binding peptides were predicted by searching for A\*2402 anchors in HIV proteins (Tyr at 2, and Phe, Leu or Ile at the C term) – 53 of the 59 peptides bound A\*2402.
- This peptide induced CTL in 3/4 HIV-1 + people tested.
- RYPLTFGWCF bound to A\*2402 strongly, the epitope can be processed in a vaccinia construct and presented – two specific CTL clones were obtained.

**HXB2 Location** Nef (134–143)**Author Location** Nef (138–147)**Epitope** RYPLTFGWCF**Epitope name** Nef138-10**Subtype** B**Immunogen** vaccine*Vector/Type:* Sendai virus vector system (SeV)**Species (MHC)** human (A\*2402)**References** Kawana-Tachikawa *et al.* 2002

- A Sendai virus vector system (SeV) was developed that expressed HLA-A\*2402-restricted class I/peptide complexes; this system could be used to detect responses and has the potential to elicit immune responses.
- MHC class I/peptide tetramers could be made using this system that bound to epitope-specific CTLs in PBMCs.
- Cells transfection with SeV modified to express A\*2402-HIV epitope complexes induced CTL mediated specific cell lysis.

**HXB2 Location** Nef (134–143)**Author Location** Nef**Epitope** RYPLTFGWCF**Epitope name** Nef138-10**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*2402)**Donor MHC** A\*2402**Country** Japan**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** binding affinity, epitope processing, immunodominance, escape**References** Furutsuki *et al.* 2004

- 70% of Japanese people carry HLA A\*2402, and the rFpIftg-wcf (2F) escape variant of this A\*2402 epitope was found to be positively selected in Japan; reversion to wild-type in HLA-A24 negative individuals occurred very slowly over years. The 2F escape variant appears to be common in Japan due to escape and then transmission of this form in the population. The mechanism of escape appeared to be in processing of Nef and antigen presentation rather than HLA binding since both wild-type and 2F variant bound to HLA-A\*2402 with almost same efficiency; the authors suggest the epitope may be cleaved at position 5 with a higher frequency when the 2F mutation is present.

**HXB2 Location** Nef (134–143)

**Author Location** Nef (134–143 BRU)

**Epitope** RYPLTFGWCY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Keywords** binding affinity, epitope processing

**References** Choppen *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- RYPLTFGWCY was recognized in 5/12 (42%) of individuals with HLA A24. It was a moderate affinity HLA-A24 binder.

**HXB2 Location** Nef (134–143)

**Author Location** Nef (134–143)

**Epitope** RYPLTFGWCY

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A24)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** Nef (134–143)

**Author Location** Nef (134–143 HXB2)

**Epitope** RYPLTFGWCY

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Country** Viet Nam

**Assay type** HLA binding

**Keywords** subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01\_AE variant rypICfgwcy had same HLA-binding score as the HXB2 epitope.

**HXB2 Location** Nef (134–143)

**Author Location** Nef

**Epitope** RYPLTFGWCF

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A\*24, A\*32, B\*07, B\*18, Cw\*07

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- Variant rFpIftg-wcf was detected in increasing frequencies in clones from an A24+ infant, but was absent in all sequences from the A24- mother at delivery, revealing selective pressure as early as 3 months of age.

**HXB2 Location** Nef (134–143)

**Author Location** Nef (134–143)

**Epitope** RYPLTFGWCY

**Immunogen** HIV-1 infection

**Species (MHC)** human (A24)

**Donor MHC** A2, A26, B51, B62; A2, B39, B60

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** HAART, ART, escape, viral fitness and reversion

**References** Asquith *et al.* 2006

- In order to reconcile apparent conflicts between a CTL-protective role as suggested by HLA-1 alleles associated with different rates of progression to AIDS, and a CTL non-protective role as suggested by the fact that virus clearance following ART is not impaired in advanced AIDS, a model is made that quantifies the efficiency of HIV-1-specific CTLs in vivo. As a surrogate for the actual rate of CTL-killing of infected cells, the model rests on calculating virus escape rate for an epitope and subtracting its reversion rate upon transmission to a non-restricting HLA bearing host. It is shown that CTLs recognizing a single epitope kill only 2% of productively infected CD4+ cells. The rate of CTL lysis was found to be significantly faster during primary infection than in chronic infection. However, the authors suggest that small differences in CTL lysis rate can translate into large differences in terms of absolute numbers of infected cells killed, which are likely to be clinically relevant.
- The best estimates of reversion rates for this epitope, RYPLTFGWCY/F, in 2 subjects were found to be -0.014 and 0.005/day with SEs of 0.
- A Y135F substitution was shown to confer escape from an A24-restricted response by prevention of epitope processing. In an HLA A24- individual, the mutation rapidly reverted to wild type. Reversion of the Y135F escape mutant was observed in a second A24- individual. The model fitted the data well, giving a rate of 0.005/day. In this subject, the 135F-138C variant was out-competed by a 135Y-138C variant rather than by the wild type (135Y-138T). The rate of reversion with respect to the wild type is zero.

**HXB2 Location** Nef (134–143)  
**Author Location** Nef (134–143 BRU)  
**Epitope** RYPLTFGWCY  
**Subtype** B, CRF02\_AG  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A24, B35)  
**Country** Cote D'Ivoire  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons  
**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 3/9 CRF02\_AG-infected Ivoirians, and 1/9 B-infected French subjects.
- A C-term F was most common in both the CRF02 and B clade infected subjects, and subjects that carried the F, RYPLTFGWCF, reacted with the peptide. One Ivoirian that recognized the peptide carried the form RfPLTFGWCF.

**HXB2 Location** Nef (134–144)  
**Author Location** Nef (134–144 LAI)  
**Epitope** RYPLTFGWCYK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B18)  
**Keywords** review, escape  
**References** Coullin *et al.* 1994; Goulder *et al.* 1997a

- Mutational variation in HIV epitopes in individuals with appropriate HLA types can result in evasion of CTL response.
- Goulder *et al.* [1997a] is a review of immune escape that summarizes this study.

**HXB2 Location** Nef (134–144)  
**Author Location** Nef (134–144)  
**Epitope** RYPLTFGWCYK  
**Epitope name** RYP  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B18)  
**Keywords** HAART, ART, acute/early infection  
**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV-1 infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- None of the 8 study subjects recognized this epitope but none were HLA B18+

**HXB2 Location** Nef (134–148)  
**Author Location** Nef  
**Epitope** RYPLTFGWCFKLVVP  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* J.Virol. 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.



- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, RYPLTFGWCFKLVVPV, had an overall frequency of recognition of 32% - 35.6% AA, 26.9% C, 31.8% H, 33.3% WI. This peptide is included in a 54 aa Nef highly reactive region to be used for vaccine design. It is also part of 'Region II', QKRQDILDWVYHTQGYPDWQNYTPGPGIRYPLTFGWCFKLVPEPEKVEEAN, a 54 aa region recognized by >90% of subjects across ethnic groups.

**HXB2 Location** Nef (135–143)

**Author Location** p17

**Epitope** YPLTFGWCF

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** Intracellular cytokine staining

**Keywords** immunodominance, genital and mucosal immunity

**References** Kaul *et al.* 2003

- Predefined immunodominant peptide responses were used to compare CD8+ T cells responses in the blood and cervix of 16 HIV+ Kenyan sex workers. Cervical responses were detected in 8/10 women from whom adequate samples could be obtained. The frequency of the CD8+ T cell response in the genital tract was comparable to the blood, with a trend toward being slightly higher.
- The immunodominant response was to this epitope in the PBMC of 1/16 patients (Kaul *et al.* 2001, AIDS, 107:1303).

**HXB2 Location** Nef (135–143)

**Author Location** Nef (135–143 LAI)

**Epitope** YPLTFGWCF

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (B\*0702)

**Keywords** epitope processing

**References** Lucchiari-Hartz *et al.* 2000

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152.
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments.
- YPLTFGWCF is the naturally processed ligand for B7, and this epitope is the only one of the five that may require trimming at the N-termini.
- YPLTFGWCF is present in low copy number in the cell, possibly due to a predominant proteasomal cleavage site between Y and P.

**HXB2 Location** Nef (135–143)

**Author Location** (C consensus)

**Epitope** YPLTFGWCF

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*18)

**Country** South Africa

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, optimal epitope

**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YPLTFGWCF is an optimal epitope for B\*5301, B\*18, and B\*35.

**HXB2 Location** Nef (135–143)

**Author Location** Nef (135–143 LAI)

**Epitope** YPLTFGWCF

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B\*1801)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is a B\*1801 epitope.

**HXB2 Location** Nef (135–143)

**Author Location** Nef (135–143 HXB2)

**Epitope** YPLTFGWCF

**Epitope name** YF9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1801)

**Donor MHC** A\*0201, A\*2501, B\*1801, B\*5101, Cw\*0102, Cw\*1203

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** escape, immune evasion, optimal epitope

**References** Liu *et al.* 2006b

- T-cell immunity and the impact of selection were longitudinally studied in a patient from the time of transmission. New epitopes were detected at sites that were shown to be under positive selection. Env was found to be the major target of CTLs and most of the new epitopes were found here. One third of the sites examined were associated with epitope escape mutations from CTL. Acquisition of mutations found at high frequency in the database was suggested to be a result of reversion of CTL epitopes in the absence of immune targeting.

**HXB2 Location** Nef (135–143)

**Author Location** Nef (135–143)

**Epitope** YPLTFGWCF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*35)

**Donor MHC** A\*03, A\*24, B\*35, B\*40

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, variant cross-recognition or cross-neutralization, superinfection

**References** Yang *et al.* 2005b

- An individual infected with a drug-resistant strain of HIV-1 subtype B with controlled viremia became superinfected with another subtype B strain. The second strain outgrew the first despite lower replication capacity and the same viral phenotype. The strains showed differences in their epitope sequences. The CTL responses to the first strain declined after superinfection, followed by some adaptation of targeting to the new epitopes of the second strain. Differences in the recognized epitopes were suggested to have contributed to the poor immune containment of the second strain.
- The response to the peptide that carried this epitope, YPLTFGWCF, was present before superinfection but waned afterward. The epitope from the second strain had a mutation, yplCf<sub>g</sub>wcf. A second overlapping epitope in the reactive peptide might be involved, the A\*24 epitope RYPLTFGWCF.

**HXB2 Location** Nef (135–143)  
**Author Location** (C consensus)  
**Epitope** YPLTFGWCF  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*35)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YPLTFGWCF is an optimal epitope for B\*5301, B\*18, and B\*35.

**HXB2 Location** Nef (135–143)  
**Author Location** Nef (135–143)  
**Epitope** YPLTFGWCF  
**Epitope name** YF9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*18, B\*35)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** assay standardization/improvement, acute/early infection, immune evasion  
**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 5 additional variants of this epitope, YPLTFGWCF, were found using the PTE-B set - fPLTFGWCF, YPLcFGWCF, fPLcFGWCF, YPLTFGW<sub>Cy</sub> and YPLTIGWCF. Only the last variant was not recognized when restricted by HLA-B\*35, though the first variant alone, fPLTFGWCF, was present as a patient autologous sequence. While no epitope variants were seen in the T-cell HLA-B\*18 restricted response, these T cells

did react with 3 out of 6 possible epitopic variants viz. YPLTFGWCF, fPLTFGWCF and YPLTFGW<sub>Cy</sub>. Each of the 6 possible variants was associated predominantly with certain HIV-1 clades: YPLTFGWCF with clades B, C, A; fPLTFGWCF with clades A, B, C; YPLTFGW<sub>Cy</sub> with clades A, C; YPLTIGWCF with clade F; fPLcFGWCF with circulating recombinant forms and YPLcFGWCF with clade B.

**HXB2 Location** Nef (135–143)  
**Author Location** Nef (135–143)  
**Epitope** YPLTFGW<sub>Cy</sub>  
**Immunogen**  
**Species (MHC)** human (B\*5301)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

**HXB2 Location** Nef (135–143)  
**Author Location** (C consensus)  
**Epitope** YPLTFGWCF  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5301)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, optimal epitope  
**References** Kiepiela *et al.* 2007

- A comprehensive analysis of 160 class I T cell responses in 578 individuals from KwaZulu-Natal, South Africa was performed. Gag-specific responses were associated with lowering viremia, while Env, accessory and regulatory protein-specific responses were associated with higher viremia.
- YPLTFGWCF is an optimal epitope for B\*5301, B\*18, and B\*35.

**HXB2 Location** Nef (135–143)  
**Author Location** Nef  
**Epitope** YPLTFGW<sub>Cy</sub>  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5301)  
**Country** Kenya  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons, cross-presentation by different HLA, variant cross-recognition or cross-neutralization  
**References** Currier *et al.* 2006

- The pattern of immunodominance and epitope clustering within Gag and Nef proteins in subtype A infected individuals was similar to that seen in subtype B and C infections. An immunodominant HLA-C restricted epitope, YVDRF-FKTL (YL9 from Gag protein) was observed and restricted to Cw0304.
- The sequence girYPLTFGW<sub>Cy</sub>fk<sub>l</sub>v is associated with HLA-B\*5301 and contains the epitope YPLTFGW<sub>Cy</sub>.

**HXB2 Location** Nef (135–143)  
**Author Location**  
**Epitope** YPLTFGW<sub>Cy</sub>  
**Epitope name** Nef-YY9

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (B\*5301, B35)**Donor MHC** A\*3002, A\*3201, B\*4501, B\*5301, Cw\*0401, Cw\*1202**Keywords** HAART, ART**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- Subject 00RCH33 was on HAART had a viral load of 2900 and CD4 count of 727 and also recognized the epitopes HIGP-GRIFY, gp160(310-318), HLA A\*3002; AETFYVDGA, RT(437-445), HLA B\*4501; and RSLYNTVATLY, p17(76-86), HLA A\*3002.
- Among HIV+ individuals who carried HLA B53, 8/15 (53%) recognized this epitope – one subject also carried B7, previously shown to restrict this epitope.
- Among HIV+ individuals who carried HLA B35, 13/19 (68%) recognized this epitope.

**HXB2 Location** Nef (135–143)**Author Location** Nef (subtype D)**Epitope** YPLTFGWCF**Subtype** D**Immunogen** HIV-1 exposed seronegative**Species (MHC)** human (B18)**References** Kaul *et al.* 2000

- 11/16 heavily HIV exposed but persistently seronegative sex-workers in Nairobi had HIV-specific CD8 gamma-IFN responses in the cervix – systemic CD8+ T cell responses tended to be to the same epitopes but at generally lower levels than cervical CD8+ T cell responses.
- Low risk individuals did not have such CD8+ cells.
- CD8+ T cell epitopes: DTVLEDINL (3 individuals), SLYNTVATL (4 individuals), LSPRTLNAW (3 individuals) and YPLTFGWCF (4 individuals) were most commonly recognized by the HIV-resistant women.

**HXB2 Location** Nef (135–143)**Author Location** Nef (135–143 LAI)**Epitope** YPLTFGWCY**Subtype** B**Immunogen** HIV-1 exposed seronegative**Species (MHC)** human (B18)**References** Culmann *et al.* 1991; Culmann-Penciolelli *et al.* 1994

- Nef CTL clones from HIV+ donors.

**HXB2 Location** Nef (135–143)**Author Location** Nef (135–143 SF2)**Epitope** YPLTFGWCY**Immunogen** HIV-1 infection**Species (MHC)** human (B18)**Keywords** HAART, ART, acute/early infection**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B18+ individuals that had a CTL response to this epitope broken down by group: 0/3 group 1, 1/2 group 2, and 0/0 group 3.

**HXB2 Location** Nef (135–143)**Author Location** Nef**Epitope** YPLTFGWCF**Immunogen** HIV-1 infection**Species (MHC)** human (B18)**Keywords** HIV exposed persistently seronegative (HEPS)**References** Kaul *et al.* 2002

- Neisseria gonorrhoea cervicitis in 9 HIV+ Kenyan sex workers caused a functional deficiency in IFN-gamma production in HIV-1 epitope-specific CD8+ T-cells, detected by intracellular cytokine production and tetramer assays, while not affecting the total number of epitope-specific CTLs.
- Ghonorrhea caused the weaker HIV-1 specific CTL responses in 4 HIV-1 exposed persistently seronegative (HEPS) women to become undetectable by Elispot and tetramer assays, and CMV-specific CTL in 2 HEPS subjects were shown to have impaired function with regard to IFN-gamma production.

**HXB2 Location** Nef (135–143)**Author Location** Nef**Epitope** YPLTFGWCY**Epitope name** B18-YY9(Nef)**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B18)**Donor MHC** A30, A32, B18, B27**Keywords** HAART, ART, supervised treatment interruptions (STI)**References** Altfeld *et al.* 2002b

- Peripheral blood (PB) and lymph node (LN) CD8+ T-cell responses were compared in 15 asymptomatic HIV-1 infected patients using all known optimal CTL epitopes (<http://hiv-web.lanl.gov/content/hiv-db/REVIEWS/brander2001.html>) for each person's class I HLA alleles.
- 60 epitope responses were detected in both PB and LN samples of the 15 patients, and an additional 8 responses were detected only in LN. The total magnitude of the response was similar in LN and PB, but the percentage of CD8+ T cells in the LN is lower so the number of HIV-specific cells per million CD8+ T-cells is higher in the LN.

- 1 year post-HAART treatment in five patients studied, the magnitude of the CD8 T-cell response was decreased in both LN and PB, but more dramatically in PB, and 13/25 epitope responses in the PB became undetectable, in contrast to 5/26 in the LN.
- Treatment interruption following HAART induced resulted in increased viremia accompanied by the restoration of the detection of 13 epitopes that had become undetectable in the PB, and the addition of 9 novel epitope responses.
- Breakdowns of epitope responses were shown for 4 individuals. Patient D displayed the greatest response to B27-KK10 (p24), and also responded to A30-RY11(p17), A32-PW10(RT), A30-KY11(RT), A32-RW10(gp120), and B18-YY9(Nef).

- HXB2 Location** Nef (135–143)  
**Author Location** Nef (135–143)  
**Epitope** YPLTFGWCY  
**Epitope name** YY9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B18)  
**Donor MHC** A11, A2, B18, B44, Cw12, Cw5  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay  
**Keywords** optimal epitope  
**References** Allen *et al.* 2005b
- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
  - This epitope did not vary.

- HXB2 Location** Nef (135–143)  
**Author Location** Nef (135–143)  
**Epitope** YPLTFGWCY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B18)  
**Donor MHC** A11, A2, B18, B44, Cw12, Cw5  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Allen *et al.* 2005a
- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - This epitope was reactive, but escape mutations did not accrue in it over time.

- HXB2 Location** Nef (135–143)  
**Author Location**  
**Epitope** YPLTFGWCY

- Immunogen** HIV-1 infection  
**Species (MHC)** human (B18)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** supertype, cross-presentation by different HLA

- References** Frahm *et al.* 2007
- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
  - Based on a prediction of the minimum number of HLA alleles needed to cover the HLA representation in all responders to this epitope, a minimum set of 6 alleles was found: 1 allele previously known to be associated (B18) and 5 additional alleles (A02, A11, A23, A24, Cw04).

- HXB2 Location** Nef (135–143)  
**Author Location**  
**Epitope** YPLTFGWCY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B18)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** supertype, cross-presentation by different HLA

- References** Frahm *et al.* 2007
- 100 HIV-infected subjects were tested for response to optimally-defined CTL epitopes regardless of the subject's HLA type. Half of all detected responses were seen in the absence of the originally reported restricting HLA class I allele, and only 3% of epitopes were recognized exclusively in the presence of their original allele. Statistical and experimental methods were used to define additional HLA alleles associated with the epitopes.
  - In addition to its known HLA association (B18), 2 additional HLAs (B35, B53) were statistically predicted to be associated with this epitope.

- HXB2 Location** Nef (135–143)  
**Author Location** (C consensus)  
**Epitope** YPLTFGWCF  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*5301, B18)  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** cross-presentation by different HLA, characterizing CD8+ T cells

- References** Kiepiela *et al.* 2004
- HLA class I restricted CD8+ T-cell responses against HIV-1 were analyzed in African patients. Significantly more responses were shown to be HLA-B restricted. Viral load, CD4 count, and thus rate of disease progression were also associated with HLA-B alleles. In addition, the selection pressure

imposed on HIV-1 by HLA-B alleles was shown to be substantially greater than by other alleles.

- This epitope was suggested to be the epitope within a longer reactive peptide based on correspondence with a known epitope in the HIV database. Also, a significantly higher frequency of people in the Durban cohort who reacted with the peptide had this HLA type.

**HXB2 Location** Nef (135–143)

**Author Location** Nef (135–143)

**Epitope** YPLTFGWCY

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human (B18, B49)

**Keywords** HIV exposed persistently seronegative (HEPS), immunodominance

**References** Kaul *et al.* 2001a

- Variants YPLTFGWC(Y/F) are specific for the B/D clades.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.
- Responses in HEPS women tended to be lower, and focused on different epitopes with HLA presenting molecules that have previously been associated with reduced risk of infection, and there was a shift in the response in the HEPS women upon late seroconversion to epitopes recognized by the HIV-1 infected women.
- 43/91 HEPS women had CD8+ responses and detection of HIV-1-specific CTL in HEPS women increased with the duration of viral exposure.
- Among HLA-B18 women, 1/4 HEPS and 8/9 HIV-1 infected women recognized this epitope, likelihood ratio 5.3, *p* value 0.04, and HEPS women tended to respond to FRDYV-DRF(Y/F)K, while infected women tended to respond to YPLTFGWC(Y/F)
- The dominant response to this HLA allele was to this epitope for the one reactive HEPS case and in all 8/9 HIV-1 infected women.
- Differences in epitope specificity were only seen for responses restricted by class I HLA alleles A2, A24, A\*6802, B14, and B18, previously shown to be associated with resistance to HIV-1 in this cohort.

**HXB2 Location** Nef (135–143)

**Author Location** Nef (139–147 SF2)

**Epitope** YPLTFGWCF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Shiga *et al.* 1996

- Binds HLA-B\*3501.

**HXB2 Location** Nef (135–143)

**Author Location** Nef (135–143 BRU)

**Epitope** YPLTFGWCY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Keywords** binding affinity, epitope processing

**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- YPLTFGWCY was recognized in 2/13 (15%) of individuals with HLA B7, and 11/14 (79%) of individuals with HLA B35, and it was a moderate affinity HLA binder.

**HXB2 Location** Nef (135–143)

**Author Location** Nef

**Epitope** YPLTFGWCY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** A11, A3, B35, B51

**Keywords** mother-to-infant transmission

**References** Sabbaj *et al.* 2002

- IFN $\gamma$  T-cell responses in breast milk of 5 HIV-1 infected women from the US and 6 from Zambia were tested with using Elispot. 11/11 women responded to Gag, 8/11 responded to Pol, 7/11 women to Nef, and 2/5 women to Env peptide pools. These responses were shown to be primarily due to CD8+ T-cells in one woman, and another woman had cytolytic responses measured by Cr-release.
- T-cells in breast milk from a volunteer who was HLA A3, A11, B35, B51 induced IFN $\gamma$  after stimulation with a peptide that carries known B35 epitope YPLTFGWCY.
- The frequencies of responses in the two compartments differed, and 2/4 women that responded to epitopes in Nef 101-205 and Pol 601-710 showed responses in breast milk but no detectable responses in peripheral blood cells.

**HXB2 Location** Nef (135–143)

**Author Location** Nef (135–143)

**Epitope** YPLTFGWCY

**Epitope name** YY9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**Donor MHC** A\*0201, A\*0301, B\*3501, B\*51, Cw\*04, Cw\*06

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay

**Keywords** escape, acute/early infection

**References** Bansal *et al.* 2005

- Patients with acute or early infection were shown to preferentially target variable peptides with higher entropy while those with chronic infection showed responses towards more conserved peptides with lower entropy. In longitudinally followed subjects, responses to variable proteins declined over time while responses to conserved proteins increased. The decline is suggested to be due to CTL escape.

- The response to this peptide was initially low, but increased over time.

**HXB2 Location** Nef (135–143)

**Author Location**

**Epitope** YPLTFGWCY

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox, canarypox prime with recombinant protein boost *Strain:* B clade BRU, B clade LAI, B clade MN, multiple epitope immunogen *HIV component:* Gag, gp120, gp41, Nef, Pol, Protease

**Species (MHC)** human (B35)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** vaccine-induced epitopes, characterizing CD8+ T cells

**References** Horton *et al.* 2006a

- CD8+ T-cell function induced by HIV-1 immunogens and natural infection was compared. Natural infections consisted of early, chronic, and long term nonprogressors.
- B27- and B57-restricted CD8+ T cells from nonprogressors exhibited greater expansion than those restricted by other alleles, providing an explanation for the observed association between HLA-B27/B57 and control of HIV-1 infection.

**HXB2 Location** Nef (135–143)

**Author Location** Nef

**Epitope** YPLTFGWCY

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B49)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 1998a

- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is identical to the B clade epitope.
- The D subtype consensus is ypltfgwcf.

**HXB2 Location** Nef (135–143)

**Author Location** Nef (subtype B)

**Epitope** YLPTFGWCY

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (B49)

**Keywords** subtype comparisons

**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- This epitope is conserved among A and B clade viruses.

- The Clade D version of the epitope, YPLTFGWCF, was preferentially recognized by CTL.

**HXB2 Location** Nef (135–143)

**Author Location**

**Epitope** YPLTFGWCY

**Immunogen** HIV-1 infection

**Species (MHC)** human (B49)

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope, YPLTFGWC(Y/F), was recognized in 1/22 HEPS sex worker controls (ML1668)

**HXB2 Location** Nef (135–143)

**Author Location** Nef (135–143)

**Epitope** YPLTFGWCF

**Immunogen**

**Species (MHC)** human (B53)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Nef (135–143)

**Author Location** Nef

**Epitope** YPLTFGWCY

**Epitope name** B53-YY9(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (B53)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (135–143)

**Author Location** Nef (135–143 BRU)

**Epitope** YPLTFGWCY

**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human (B7)**Keywords** binding affinity, epitope processing**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- YPLTFGWCY was recognized in 2/13 (15%) of individuals with HLA B7, and 11/14 (79%) of individuals with HLA B35, and it was a moderate affinity HLA binder.

**HXB2 Location** Nef (135–143)**Author Location** Nef (135–143)**Epitope** YPLTFGWCY**Subtype** B**Immunogen** vaccine*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21**Species (MHC)** human (B7 supertype)**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the most frequently recognized of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** Nef (135–143)**Author Location** Nef (135–143)**Epitope** YPLTFGWCY**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B18, B35, B49, B53, B7)**Donor MHC** A3, A31, B18, B39; A1, A3, B35, B8**Country** United States**Assay type** Intracellular cytokine staining, Flow cytometric T-cell cytokine assay**Keywords** HAART, ART, escape, variant cross-recognition or cross-neutralization**References** Casazza *et al.* 2005

- Evidence of continued viral evolution during HAART therapy despite low viral load was found in 1/5 patients studied.

- A predominant sequence of ypltfgwcf was found in 2 patients (in 11/11 and 15/15 sequences) that cross-recognized the peptide used for screening, YPLTFGWCY. In patient B, CD8 T-cell response of 0.95% was found for the dominant variant, while the response for the screening epitope ypltfgwcy was 0.58%. In patient F, the frequency of response did not differ significantly between the 2 variants. Assays for both patients were done immediately prior to the initiation of therapy.

**HXB2 Location** Nef (135–143)**Author Location** Nef (135–143 BRU)**Epitope** YPLTFGWCY**Subtype** B, CRF02\_AG**Immunogen** HIV-1 infection**Species (MHC)** human (B18, B53, B7)**Country** Cote D'Ivoire**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons**References** Inwoley *et al.* 2005

- CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivoirians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivoirian subjects.
- This epitope was recognized by 3/9 CRF02\_AG-infected Ivoirians, and 0/9 B-infected French subjects.
- The three Ivoirians that recognized this peptide carried three different variants of the epitope: identical to LAI: YPLTFGWCY, YPLTFGWcf, and fPLTFGWcf. 6/8 Ivoirians carried a variant, 5/5 B clade infections were not identical.

**HXB2 Location** Nef (135–143)**Author Location** Nef (134–)**Epitope** YPLTFGWCF**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (Cw\*0401)**Country** India**Assay type** Other**Keywords** subtype comparisons**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope YPLTFGWCF, is predicted to bind HLA-Cw\*0401 with a binding affinity score of 40.

**HXB2 Location** Nef (136–144)**Author Location** Nef (136–144 BRU)**Epitope** PLTFGWCYK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A3)**Keywords** binding affinity, epitope processing**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- PLTFGWCYK was recognized in 3/12 (25%) of individuals with HLA A3. It was a low affinity HLA-A3 binder.

**HXB2 Location** Nef (136–145)

**Author Location** Nef (136–145)

**Epitope** PLTFGWCYKL

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A\*0201)

**Keywords** binding affinity, dendritic cells, Th1

**References** Wilson *et al.* 1999b

- Dendritic cells are the most potent for priming T cell responses – DCs can stimulate autologous CTL responses from T cells cultured from HIV negative donors.
- Th1-biasing cytokines IL-12 or IFN alpha enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within.
- B7 and A2 Nef epitopes were studied and the relative binding affinity of A2 epitopes for A2 was: PLTFGWCYKL greater than VLEWRFD SRL which was much greater than AFHH-VAREL.
- Noted in Brander *et al.*, 1999 this database, to be A\*0201.

**HXB2 Location** Nef (136–145)

**Author Location** Nef (136–145 LAI)

**Epitope** PLTFGWCYKL

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*0201)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0201 epitope.

**HXB2 Location** Nef (136–145)

**Author Location** Nef (136–145 LAI)

**Epitope** PLTFGWCYKL

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A\*0201)

**Keywords** epitope processing

**References** Lucchiari-Hartz *et al.* 2000

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152.
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments.

- The CTL that recognized PLTFGWCYKL also recognized PLTFGWCYKLV, and both forms of the epitope are naturally processed and both seem to be the direct product of a proteasomal digest, although in low copy number.

**HXB2 Location** Nef (136–145)

**Author Location** Nef (136–145)

**Epitope** PLTFGWCYKL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** Th1, characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Three of seven patients responded to this peptide with GzB producing cells and three of the patients responded with IFN-gamma producing cells. Only one patient had both a GzB and IFN-gamma response.

**HXB2 Location** Nef (136–145)

**Author Location** Nef

**Epitope** PLTFGWCFKL

**Epitope name** P10L

**Immunogen** vaccine

*Vector/Type:* measles virus (MV) *Strain:* multiple epitope immunogen *HIV component:* gp140, gp140 $\Delta$ V3

**Species (MHC)** transgenic mouse (A\*0201)

**Assay type** Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** memory cells, vaccine antigen design, antibody generation, characterizing CD8+ T cells

**References** Lorin *et al.* 2005

- A recombinant measles MVSchw virus expressing an HIV-1-derived polyepitope effectively primed HLA-A\*0201-restricted CTL responses against multiple conserved HIV-1 epitopes in HLA-A\*0201 transgenic mice. Also, a recombinant MVSchw virus expressing gp140 with deleted V1, V2, and V3 loops successfully induces neutralizing antibodies against HIV-1. A live attenuated measles vaccine could provide a safe and efficient pediatric vaccination vector for simultaneous vaccination against HIV and measles.

**HXB2 Location** Nef (136–145)

**Author Location** Nef (136–145)

**Epitope** PLTFGWCFKL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Durali *et al.* 1998



- Cross-clade CTL response was studied by determining the CTL activity in seven patients from Bangui, (6 A subtype, and 1 AG recombinant infections) and one A subtype infection from a person living in France originally from Togo, to different antigens expressed in vaccinia.
- Pol reactivity: 8/8 had CTL to A subtype, and 7/8 to B subtype, and HIV-2 Pol was not tested.
- Gag reactivity: 7/8 reacted with A or B subtype gag, 3/8 with HIV-2 Gag.
- Nef reactivity: 7/8 reacted with A subtype, and 5/8 with B subtype, none with HIV-2 Nef.
- Env reactivity: 3/8 reacted with A subtype, 1/8 with B subtype, none with HIV-2 Env.
- Patient B18 had the greatest breadth and diversity of response, and recognized Gag SLYNTVATL and Nef PLTFGWCFKL.

**HXB2 Location** Nef (136–145)

**Author Location** Nef (157–166)

**Epitope** PLTFGWCFKL

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost

**Species (MHC)** human (A2)

**References** Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D<sup>d</sup> – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCFKL), Pol 346-354 (VIYQYMDLL), and Nef 180-189 (VLEWRFD-SRL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- PLTFGWCFKL was recognized by 1 of the HLA-A2 patients.

**HXB2 Location** Nef (136–145)

**Author Location** Nef (135–144 93TH253 subtype CRF01)

**Epitope** PLTFGWCFKL

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although

E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.

- 0/4 tested FSWs recognized the E clade version of this epitope PLCFGWCFKL, which differs from the previously defined B clade version by two amino acids, PLTFGWCFKL.
- This epitope was only conserved in CRF01 (subtype E) and subtype B.

**HXB2 Location** Nef (136–145)

**Author Location** Nef (136–145)

**Epitope** PLTFGWCFKL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

**HXB2 Location** Nef (136–145)

**Author Location**

**Epitope** PLTFGWCFKL

**Epitope name** Nef-PL10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**References** Sabbaj *et al.* 2003

- Among HIV+ individuals who carried HLA A02, 3/29 (10%) recognized this epitope.

**HXB2 Location** Nef (136–145)

**Author Location** Nef (136–145 BRU)

**Epitope** PLTFGWCFKL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** binding affinity, epitope processing

**References** Choppin *et al.* 2001

- Seventy-three 8-11 mer peptides were generated based on putative anchor motifs in the Nef BRU sequence for HLA A2, A3, A24, B7, B8, and B35; these 73 peptides had 81 motifs. 54% bound to the predicted HLA molecule, particularly A2, B7/35, and B8. The strength of HLA-peptide binding was not directly related to the number of individuals that recognized a protein.
- 20s proteasome cleavage of the Nef protein positions 66-100 showed a large fraction of peptides were cleaved ending at: 87L, 83A, 81Y, 71P, 68F and 67G. The frequency of recognition may be in part dictated by the cleavage step in processing.
- PLTFGWCFKL was recognized in 9/28 (32%) of individuals with HLA A2. It was a low affinity HLA-A2 binder.

**HXB2 Location** Nef (136–145)

**Author Location** Nef (136–145)

**Epitope** PLTFGWCYKL**Subtype** B**Immunogen** vaccine*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21**Species (MHC)** human (A2)**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This was one of the most highly recognized of the 31 peptides that were shown to elicit a response.

**HXB2 Location** Nef (136–145)**Author Location** Nef (136–145)**Epitope** PLTFGWCYKL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding**Keywords** acute/early infection, optimal epitope**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized in chronic infection.

**HXB2 Location** Nef (136–145)**Author Location** Nef (136–145 HXB2)**Epitope** PLTFGWCYKL**Subtype** B, CRF01\_AE**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Country** Viet Nam**Assay type** HLA binding**Keywords** subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design**References** Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01\_AE variant pICfgwcfkl had a higher HLA-binding score than the HXB2 epitope.

**HXB2 Location** Nef (136–145)**Author Location** Nef**Epitope** PLTFGWCYKL**Epitope name** A2-PL11(Nef)**Immunogen** HIV-1 infection**Species (MHC)** human (A2)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression, immunodominance, early-expressed proteins**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (136–146)**Author Location** Nef (136–146 LAI)**Epitope** PLTFGWCYKLV**Subtype** B**Immunogen** in vitro stimulation or selection**Species (MHC)** human (A\*0201)**Keywords** epitope processing**References** Lucchiari-Hartz *et al.* 2000

- Five naturally processed MHC class I ligands were identified in Nef in the conserved immunogenic region Nef between 123-152.
- All five could be transported by TAP, and 4/5 had N-termini that were major cleavage points for the proteasome, only one had extended precursor fragments.
- The CTL that recognized PLTFGWCYKLV also recognized PLTFGWCYKLV, and both forms of the epitope are naturally processed and both seem to be the direct product of a proteasomal digest, although in low copy number.

**HXB2 Location** Nef (137–145)**Author Location** Nef (137–145)**Epitope** LTFGWCFKL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A\*02)**Country** United States**Assay type** Intracellular cytokine staining, Other**Keywords** rate of progression, escape, immune evasion**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

**HXB2 Location** Nef (137–145)

**Author Location** Nef (139–147 HXB3)

**Epitope** LTFGWCFKL

**Immunogen** vaccine

*Vector/Type:* DNA, peptide *Strain:* B clade HXB3 *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (A\*0201)

**Keywords** binding affinity, computational epitope prediction

**References** Sandberg *et al.* 2000

- Ten Nef 9-mer peptides were predicted to have a strong binding affinity with HLA-A\*0201 – of these, four did bind strongly by a T2 class I stabilization assay, several others bound weakly.
- A CTL immune response to only 3/10 peptides was detected by a 51Cr-release assay after immunization of HLA-A201 transgenic mice with either nef DNA under the control of a CMV promoter, coated on gold particles delivered to abdominal skin by gene gun – LTFGWCFKL did not elicit a CTL response.
- LTFGWCFKL was also tested by subcutaneous injection of Nef peptides in Freund's adjuvant, because it bound strongly to HLA-A\*0201, and the peptide vaccination did elicit a response.
- The lack of response to the nef DNA vaccine and the response to the peptide suggests LTFGWCFKL may not be processed.

**HXB2 Location** Nef (137–145)

**Author Location** Nef (137–145)

**Epitope** LTFGWCFKL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Other, HLA binding

**Keywords** vaccine-specific epitope characteristics, cross-presentation by different HLA, HLA associated polymorphism

**References** Reche *et al.* 2006

- 25 CTL epitopes with sequence conservation were studied. Population protection coverage (PPC) for 5 different ethnic groups in the US was estimated by combining HLA binding predictions and known HLA frequencies. HIV-1-naive individuals mounted a better response to the epitope pools than HIV-1 infected individuals.
- A more detailed evaluation of HIV-naive T-cell responses was undertaken, limiting the study to only those peptides that are restricted to A\*0201. Though the peptides could cross-recognize and bind different HLA, they were able to specifically lyse only cells of the same (A\*0201) HLA-restriction. Thus, the CTL response was less degenerate than peptide binding to MHC.
- This epitope, LTFGWCFKL, was predicted to be restricted by HLA A\*0201.

**HXB2 Location** Nef (137–145)

**Author Location** Nef (137–)

**Epitope** LTFGWCFKL

**Epitope name** Nef137

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, subtype comparisons, computational epitope prediction

**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- 3/17 HIV-infected HLA-A2+ people recognized this epitope.

**HXB2 Location** Nef (137–145)

**Author Location** Nef (137–145)

**Epitope** LTFGWCFKL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (A2)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This was one of the most highly recognized of the 31 peptides that were shown to elicit a response.

**HXB2 Location** Nef (137–145)  
**Author Location** Nef (137–145)  
**Epitope** LTFGWCFKL  
**Epitope name** Nef137-145  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** responses in children, immunodominance, characterizing CD8+ T cells  
**References** Chandwani *et al.* 2004

- Responses to five HLA-A2 presented epitopes in Nef were characterized in a population of 19 HIV infected adults and 21 children. The CD8 T-cell response to Nef was stronger and broader in adults than children, averaging 652 and 87 SFCs/10<sup>6</sup> PBMC, and 2.6 and 0.9 recognized epitopes per person, respectively.
- This epitope was second in an immunodominance hierarchy of the five A02 Nef epitopes studied.

**HXB2 Location** Nef (137–145)  
**Author Location** Nef (158–166)  
**Epitope** LTFGWCFKL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2 supertype)  
**Keywords** supertype, rate of progression  
**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802)

**HXB2 Location** Nef (137–145)  
**Author Location** Nef (136–)  
**Epitope** LTFGWCFKL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*0205, A2)  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons  
**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian subclade. Potential epitopes were computationally predicted within these Nef proteins.
- This epitope LKWKFDSQL, is predicted to bind 60% of the HLA molecules screened including HLA-A2 with a binding affinity score of 421.363, HLA-A\*0201 with a score of 10.824 and HLA-A\*0205 with a score of 4.284.

**HXB2 Location** Nef (137–145)  
**Author Location** Nef  
**Epitope** LTFGWCFKL  
**Epitope name** LL9  
**Subtype** B, C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1517, B57)  
**Donor MHC** A\*36, A\*66, B\*1517, B\*53, Cw\*04, Cw\*06; A\*02, A\*23, B\*35, B\*57, Cw\*04, Cw\*07  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** cross-presentation by different HLA, optimal epitope  
**References** Frahm *et al.* 2005

- HLA-B63-positive subjects were shown to be able to generate CTL responses early in acute HIV infection and to control HIV replication in the absence of antiretroviral treatment. Since HLA-B63 shares the epitope binding motif of HLA-B57 and -B58, it was shown that HLA-B63-positive individuals mounted CTL responses to previously identified B57-restricted epitopes, as well as novel, B63-restricted epitopes. Moreover, these novel B63-restricted epitopes can also be presented by HLA-B57 and -B58.
- Optimal epitope was defined in 2 people, 1 carrying HLA-B\*1517(B63), the other carrying B57.

**HXB2 Location** Nef (137–145)  
**Author Location**  
**Epitope** LTFGWCFKL  
**Immunogen**  
**Species (MHC)** human (B57)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes that this is an B57 epitope.

**HXB2 Location** Nef (137–145)  
**Author Location**  
**Epitope** LTFGWCFKL  
**Immunogen**  
**Species (MHC)** human (B63)  
**Keywords** optimal epitope  
**References** Frahm *et al.* 2008

- C. Brander notes that this is an B63 epitope.

**HXB2 Location** Nef (137–145)  
**Author Location** Nef (135–)  
**Epitope** LTFGWCFKL  
**Subtype** A  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons  
**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian subclade. Potential epitopes were computationally predicted within these Nef proteins.

- Of the most common HLA in India tested, this epitope, LTFGWCFKL, is predicted to associate with 60% of them.

**HXB2 Location** Nef (137–145)

**Author Location** Nef (139–)

**Epitope** LTFGWCFKL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope, LTFGWCFKL, is predicted to bind 60% of them with high affinity.

**HXB2 Location** Nef (137–146)

**Author Location** Nef (137–146)

**Epitope** LTFGWICYKLV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*6901)

**Country** India

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, immunodominance

**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa.
- 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef.
- 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.
- Epitope LTFGWICYKLV showed some conservation to subtypes A and non-Indian C.

**HXB2 Location** Nef (137–146)

**Author Location** Nef

**Epitope** LTFGWCFKL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A02)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, immunodominance, optimal epitope

**References** Bihl *et al.* 2006

- CTL responses were tested for both HIV-1 and EBV derived epitopes restricted by HLA-A, -B and -C alleles. HLA-B alleles more frequently induce detectable responses and that the responses are generally of greater magnitude than those for HLA-A and -C alleles.

- The magnitude and frequency of CTL recognition were related to each other and that TCR avidity for HLA/peptide complexes is a more important determinant for magnitude of response than peptide binding affinity to HLA.
- EBV response patterns were not significantly altered by HIV coinfection.
- Epitope LTFGWCFKL elicited a magnitude of response of 60 SFC with a functional avidity of 0.05nM.

**HXB2 Location** Nef (137–146)

**Author Location** Nef (221A)

**Epitope** LTFGWCFKL

**Epitope name** Nef-221a

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** binding affinity, subtype comparisons, super-type, computational epitope prediction

**References** Altfeld *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- 1/22 individuals with chronic HIV-1 infection recognized this epitope in ELISPOT.
- 2/12 acutely infected individuals recognized this epitope.
- LTFGWCFKL binds to five HLA-A2 supertype alleles: A\*0203, A\*0201 (highest affinity), A\*0206, A\*6802 and A\*0202.

**HXB2 Location** Nef (137–146)

**Author Location** Nef (137–146)

**Epitope** LTFGWCFKL

**Epitope name** LV10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** optimal epitope

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct

T-cell receptor and did not exhibit any cross-reactivity against the wildtype.

- This epitope did not vary.

**HXB2 Location** Nef (137–146)

**Author Location** Nef (137–146)

**Epitope** LTFGWCFKLV

**Epitope name** LV10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Flow cytometric T-cell cytokine assay

**Keywords** escape, TCR usage, variant cross-recognition or cross-neutralization, characterizing CD8+ T cells

**References** Allen *et al.* 2005b

- 4/14 optimal HIV-1 T-cell epitopes in a subject underwent mutation associated with dramatic loss of the original CD8 response. For 1 of the escape variants, a novel CD8 T-cell response equal in magnitude to the wildtype, was generated. CD8 T-cell recognizing the variant epitope utilized a distinct T-cell receptor and did not exhibit any cross-reactivity against the wildtype.
- This epitope did not vary over time.

**HXB2 Location** Nef (137–146)

**Author Location** Nef (137–146)

**Epitope** LTFGWCFKLV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Donor MHC** A11, A2, B18, B44, Cw12, Cw5

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Nef (137–146)

**Author Location** Nef (135–146)

**Epitope** LTFGWCFKLV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding

**Keywords** acute/early infection, optimal epitope

**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized during chronic infection.

**HXB2 Location** Nef (137–146)

**Author Location** Nef (158–167)

**Epitope** LTFGWCFKLV

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2 supertype)

**Keywords** supertype, rate of progression

**References** Propato *et al.* 2001

- Long-term nonprogressors (LTNPs) had strong memory resting CD8+ T-cell responses against the majority of epitopes tested, (18 for the A2 supertype, 16 for the A3 supertype) while the effector cells of long-term nonprogressors recognized far fewer epitopes.
- Progressors had memory resting CD8+ T-cells that recognized far fewer epitopes than LTNPs.
- A positive correlation between effector CD8+ T-cells and plasma viremia and a negative correlation between CD8+ effector T-cells and CD4+ T-cells was observed, which may contribute to the inability of LTNPs to clear virus.
- This epitope can bind all five HLA-A2 supertypes alleles (A\*0201, A\*0202, A\*0203, A\*0206 and A\*6802)
- Tetramer staining with A2, beta2microglobulin, and either SLYNTVATL, KLVGKLNWA, or LTFGWCFKL revealed that tetramers detected more HIV-specific cells in LTNP than in progressors, activated effector cells were the minority population, and ELISPOT correlated better with the effector cell subpopulation than the total tetramer stained population.

**HXB2 Location** Nef (138–146)

**Author Location** Nef (137–)

**Epitope** TFGWCFKLV

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0401)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope TFGWCFKLV, is predicted to bind HLA-Cw\*0401 with a binding affinity score of 25.

**HXB2 Location** Nef (141–148)

**Author Location** Nef (141–)

**Epitope** WCFKLVVPV

**Epitope name** Nef141

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* peptide *HIV component:* Nef

*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (A2)

- Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay
- Keywords** binding affinity, subtype comparisons, computational epitope prediction
- References** Corbet *et al.* 2003
- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
  - This peptide was an intermediate A2 binder, and induced a CD8+ T-cell IFN gamma response in 1/6 mice. Responses were detected in 2/17 HIV+ HLA-A2 subjects.
- HXB2 Location** Nef (144–152)
- Author Location** Nef (146–)
- Epitope** KLVPVDPEL
- Subtype** B
- Immunogen** HIV-1 infection
- Species (MHC)** human
- Country** India
- Assay type** Other
- Keywords** subtype comparisons
- References** Kumar *et al.* 2006a
- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian subclade. Potential epitopes were computationally predicted within these Nef proteins.
  - Of the most common HLA in India tested, this epitope, KLVPVDPEL, is predicted to bind 60% of them with high affinity.
- HXB2 Location** Nef (153–167)
- Author Location** Nef
- Epitope** VEEANEGENNSLLHP
- Epitope name** nef-5177
- Subtype** B
- Immunogen** HIV-1 infection
- Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)
- Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16
- Country** United States
- Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other
- Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
- References** Reinis *et al.* 2007
- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
  - LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
  - All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
  - This Nef overlapping peptide, VEEANEGENNSLLHP was mutated in the daughter D2 isolate to VEEANEGETnLLsP.
- HXB2 Location** Nef (157–165)
- Author Location** Nef (156–)
- Epitope** NEGENNCLL
- Subtype** C
- Immunogen** HIV-1 infection
- Species (MHC)** human (A\*0205, B7)
- Country** India
- Assay type** Other
- Keywords** subtype comparisons
- References** Kumar *et al.* 2006a
- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian subclade. Potential epitopes were computationally predicted within these Nef proteins.
  - Of the most common HLA in India tested, this epitope NEGENNCLL, is predicted to bind HLA-A\*0205 with a binding affinity score of 2.94.
- HXB2 Location** Nef (157–171)
- Author Location** Nef
- Epitope** NEGENNSLLHPMSLH
- Epitope name** nef-5178
- Subtype** B
- Immunogen** HIV-1 infection
- Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)
- Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16
- Country** United States
- Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other
- Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism
- References** Reinis *et al.* 2007
- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
  - Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.

- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, NEGENNSSLHPMSLH was mutated in the daughter D2 isolate to NEGETnNLLsPMSLH.

**HXB2 Location** Nef (160–174)

**Author Location** Nef (160–174)

**Epitope** ENNSLLHPMSLHGMD

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A23, B62

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- ENNSLLHPMSLHGMD is a previously unpublished epitope.

**HXB2 Location** Nef (161–175)

**Author Location** Nef

**Epitope** NNSLLHPMSLHGMD

**Epitope name** nef-5179

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.

- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, NNSLLHPMSLHGMD was mutated in the daughter D2 isolate to tNnLLsPMSLHGMeD.

**HXB2 Location** Nef (162–181)

**Author Location** Nef (161–180)

**Epitope** TSLLLHPVSLHGMDPPERVL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1995

- HIV-specific CTL lines developed by *ex vivo* stimulation with peptide.

**HXB2 Location** Nef (162–181)

**Author Location** Nef (161–180 SF2)

**Epitope** TSLLLHPVSLHGMDPPERVL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- One of these 11 had CTL response to this peptide.

**HXB2 Location** Nef (162–181)

**Author Location** Nef (101–120 SF2)

**Epitope** TSLLLHPVSLHGMDPPERVL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997b

- CTL expanded *ex vivo* were later infused into HIV-1 infected patients.

**HXB2 Location** Nef (162–181)

**Author Location** Nef (161–180 SF2)

**Epitope** TSLLLHPVSLHGMDPPERVL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- One of these 11 had CTL response to this peptide.

**HXB2 Location** Nef (165–179)

**Author Location** Nef

**Epitope** LHPMSLHGMDDPERE

**Epitope name** nef-5180

**Subtype** B



**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)  
**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism  
**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, LHPMSLHGMDPERE was mutated in the daughter D2 isolate to LsPMSLHGMeDPEKe.

**HXB2 Location** Nef (166–177)  
**Author Location** Nef (160–179 SF2)  
**Epitope** HPVSLHGMDPE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B35)  
**Keywords** HAART, ART, acute/early infection  
**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-B35+ individuals that had a CTL response to this epitope broken down by group: 1/2 group 1, 0/2 group 2, and 0/1 group 3.

**HXB2 Location** Nef (169–183)  
**Author Location** Nef  
**Epitope** SLHGMDPEREVLEW  
**Epitope name** nef-5181

**Subtype B**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)  
**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism  
**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, SLHGMDPEREVLEW was mutated in the daughter D2 isolate to SLHGMeDPEKELvW.

**HXB2 Location** Nef (172–191)  
**Author Location** Nef (171–190 SF2)  
**Epitope** GMDDPEREVLEWRFSRLAF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2, B21.

**HXB2 Location** Nef (175–184)  
**Author Location** Nef (175–184)  
**Epitope** DPEKEVLQWK  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**References** Jin *et al.* 2000b

- This a B7 epitope, a subdominant CTL response, was defined by an un-conventional approach used to predict epitopes in an HLA B7+ long-term non-progressor.
- Three additional sub-dominant HLA B7 epitopes were defined using EpiMatrix, a non-anchor based strategy for defining potential epitopes, which highlighted 2078 possible epitopes in the autologous HIV-1 derived from the study subject, followed by B7 anchor residue prediction which narrowed the set to 55

peptides, three of which could serve as functional CTL epitopes.

**HXB2 Location** Nef (175–184)  
**Author Location** Nef  
**Epitope** DPEKEVLQWK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B7)  
**Donor MHC** A\*0301, A\*2301, B\*0702, B\*1503  
**Country** United States  
**Keywords** escape, acute/early infection  
**References** Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- K to E mutation was observed in position 10.

**HXB2 Location** Nef (175–189)  
**Author Location** Nef (175–189)  
**Epitope** DPEREVLEWRFSRL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** B\*1503, B35, B7 supertype, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** computational epitope prediction, vaccine-induced epitopes  
**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- DPEREVLEWRFSRL is a previously unpublished epitope that varies from the consensus at position 10 (arginine).

**HXB2 Location** Nef (176–193)  
**Author Location** Nef  
**Epitope** PEKEVLVWKFDSRLAFHH  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Barbados, Haiti, United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other  
**Keywords** binding affinity, immunodominance  
**References** Frahm *et al.* 2004

- To identify HLA-independent immunodominant regions in HIV clade B across different ethnicities, the authors analyzed CTL responses to HIV in African-American (AA), Caucasian (C), Hispanic (H) and West Indian (WI) cohorts, and analyzed factors influencing immune dominance. Host HLA-A11 and -A25 distributions differed among ethnicities significantly; but the virus regions most targeted by CTLs in breadth and magnitude were in Gag, Nef and Int proteins (Nef-76, most targeted). Pro was the least targeted. 88% of peptides across the entire HIV sequence elicited CTL responses. 6 peptides tested were most differentially targeted between ethnicities. 3 frequently targeted and 10 highly CTL-reactive regions across all 4 ethnicities were noted for vaccine design purposes.
- Suppressive treatment rather than treatment itself was found to diminish CTL responses, whose breadth and magnitude correlates with CD4 count and not viral load. Factors found to determine peptide recognition by CTLs were (i) conserved peptides displaying low entropy (ii) low fraction of forbidden amino acids and (iii) high proteasomal cleavage score, confirming previous informatic studies [Yusim *et al.* *J. Virol.* 76:8757-68 (2002)]. These 3 variables did not correlate with each other but an inverse trend was seen between cleavage score and entropy.
- In addition, since all ethnicities were able to mount CTL responses to every HIV protein and only <12% of peptides were not recognized by any subject, the consensus sequence-based approach to vaccine design is substantiated.
- This immunodominant, frequently targeted overlapping peptide, PEKEVLVWKFDSRLAFHH, had an overall frequency of recognition of 15.3% - 22% AA, 11.5% C, 18.2% H, 9.5% WI.

**HXB2 Location** Nef (177–185)  
**Author Location** Nef (176–)  
**Epitope** HREVLKWKWF  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*2702, B\*2705)  
**Country** India  
**Assay type** Other  
**Keywords** subtype comparisons  
**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope HREVLKWKWF, is predicted to bind HLAs - B\*2702 and B\*2705 with binding affinity scores of 500 and 1000.

**HXB2 Location** Nef (179–193)  
**Author Location** Nef (175–189)  
**Epitope** EVLQWKFDSRLALRH  
**Epitope name** WF9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Donor MHC** B\*1503, B35, B7 supertype, Cw7  
**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide EVLqWKFDSSLAlrH is a variant at positions 4, 13 and 14 from the consensus peptide EREVLEWKFDSSLAF.

**HXB2 Location** Nef (180–188)

**Author Location** Nef (179–)

**Epitope** VLKWKFDSSQ

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (B8)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian subclade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope VLKWKFDSSQ, is predicted to bind HLA-B8 with a binding affinity score of 1.6.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189)

**Epitope** VLEWRFDSSL

**Epitope name** VL10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*02)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naive subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol.

Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.

- This epitope, VLEWRFDSSL, was primarily recognized as wild type. Other variants seen were VLEWRFDSSsL, VLEWRFDgSRL and the 184K emerging variant VLEWkFDSSL. Position 184 fell under 2 overlapping CTL responses restricted by HLAs A2 and B15.
- In Table 2, epitope VLvWRFDSSL is printed as the epitope studied. We chose to record the epitope as VLEWRFDSSL seen twice elsewhere in this paper, as it is more commonly annotated as such in the literature.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189 LAI)

**Epitope** VLEWRFDSSL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**References** Haas *et al.* 1996; Haas *et al.* 1997

- There was a high degree of variation in three CTL epitopes in Nef in four slow and non-progressors, and variant specific CTLs arose over time to eliminate variants, indicating immune selection.
- Noted in Brander *et al.*, 1999 this database, to be A\*0201.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189 LAI)

**Epitope** VLEWRFDSSL

**Subtype** B

**Immunogen**

**Species (MHC)** human (A\*0201)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

- C. Brander notes this is an A\*0201 epitope.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189 LAI)

**Epitope** VLMWQFDSSL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* natural variants *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** transgenic mouse (A\*0201)

**Keywords** binding affinity, vaccine-specific epitope characteristics

**References** Boissonnas *et al.* 2002

- Ten naturally occurring variants of this epitope were tested for their affinity to HLA-A\*0201 and for their ability to induce gamma-IFN and cytotoxic functions through vaccination of HLA-A\*0201 transgenic mice.

- Only two variants could induce vaccine responses: VLMWQFDSRL, a high affinity binder, and VLQWRFDSSL a medium affinity binder to A\*0201.
- In vivo priming with Nef peptide VLMWQFDSRL induced cross-reactive CTL to 6/7 peptides tested (AlmwKfdsKI, vlmwKfdsrl, vlmwKfdsKI, vIQwRfdsKI, vIVwrfdTrl, and vIAwKLdsrl but not the LAI peptide vIEwrfdsrl)
- In vivo priming with Nef peptide VLQWRFDTRL induced cross-reactive CTL to 3/6 variant Nef peptides (vIMwQfdsrl, vlqwrfdSrl and vIEwrfdsrl).

**HXB2 Location** Nef (180–189)

**Author Location** Nef (190–198)

**Epitope** VLEWRFDSSL

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* HIV-1

**Species (MHC)** mouse (A\*0201)

**Keywords** epitope processing, vaccine-specific epitope characteristics, immunodominance

**References** Singh *et al.* 2002; Sykes & Johnston 1999

- C3H (H-2k) transgenic mice carrying a fused HLA-A\*0201 alpha1 and alpha2 and H-2Dk alpha3 hybrid class I molecule were immunized using an epidermal gene gun with an ubiquitin expression library of 32 plasmids that spanned the HIV-1 genome. Ubiquitin targets the expressed HIV-1 peptides to the proteasome.
- A single immunization with the UB-HIV-1 library vaccine induced potent, stable and multivalent CTL responses against all library members.
- Immunodominant epitopes SLYNTVATL (Gag), ILKEPVHGV (Pol), RIQRGPGRAFTIGK (Env) and AFHHVAREK (Nef) elicited strong CD8+/IFN- responses and stimulated CTL that were functional in a Cr-release assay and against wild type antigen.
- The presence of multiple plasmids HLA-A\*0201-restricted CTL epitopes did not decrease CTL immunogenicity, and CTL responses to single peptide immunizations were comparable to responses based on mixtures of either 16 or 32 peptides.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189)

**Epitope** VLEWRFDSSL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B

**Keywords** Th1, characterizing CD8+ T cells

**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Three of seven patients responded to this peptide with GzB producing cells, while one of the three patients responded with IFN-gamma producing cells.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189)

**Epitope** VLEWRFDSSL

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A2)

**Keywords** binding affinity, dendritic cells, Th1

**References** Wilson *et al.* 1999b

- Dendritic cells are the most potent for priming T cell responses – DCs can stimulate autologous CTL responses from T cells cultured from HIV negative donors.
- Th1-biasing cytokines IL-12 or IFN alpha enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within.
- B7 and A2 Nef epitopes were studied and the relative binding affinity of A2 epitopes for A2 was: PLTFGWCYKL greater than VLEWRFDSSL which was much greater than AFHHVAREL.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189)

**Epitope** VLEWRFDSSL

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost

**Species (MHC)** human (A2)

**References** Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D<sup>d</sup> – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSSL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- VLEWRFDSSL was recognized by 2 of the HLA-A2 patients.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189 LAI)

**Epitope** VLEWRFDSSL

**Epitope name** N3

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART

**References** Mollet *et al.* 2000

- A panel of 16 epitopes covering 15 class I alleles was tested in 14 HIV+ patients from an unselected Caucasian population treated with HAART, using CD8+ cell IFN $\gamma$  production to measure responses.
- In general, during the first month of treatment viral load decreased and frequencies of HIV-specific CTL tripled and broadened – eight new HIV specificities that were not previously detectable were newly detected, as were CMV specific CD8+ PBL – but with continued viral suppression, HIV-specific responses diminished.
- Viral rebounds gave different patterns of response: increases or decreases in pre-existing response, new specificities, or no change.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (179–188 93TH253 subtype CRF01)

**Epitope** VLEWRFDSSL

**Subtype** CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** subtype comparisons

**References** Bond *et al.* 2001

- More than half of a cohort of HIV+ female sex workers (FSW) from Northern Thailand were HLA-A11 positive, and this study concentrated on A11 epitopes in this group, although E clade versions of previously defined B-clade A2 and A24 epitopes were also tested.
- 0/4 tested FSWs recognized the E clade version of this epitope VLIWKFDSSAL, which differs from the previously defined B clade version by three amino acids, VLEWRFDSSL.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189)

**Epitope** VLEWRFDSSL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** rate of progression, acute/early infection

**References** Day *et al.* 2001

- The CTL response to optimally defined CTL epitopes restricted by HLA class I A and B alleles in individuals who coexpressed HLA A2, A3, and B7 was studied in eight HIV-1-infected subjects, two with acute infection, five with chronic, and one long-term non-progressor (LTNP)
- 2 to 17 epitopes were recognized in a given individual, A2-restricted CTL response tended to be narrow and never dominated the response, and 25/27 epitopes were targeted by at least one person.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (178–187)

**Epitope** VLEWRFDSSL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- 5/19 patients recognized this epitope.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189)

**Epitope** VLEWRFDSSL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, HLA binding

**Keywords** acute/early infection, optimal epitope

**References** Altfeld *et al.* 2005

- The most frequently targeted HLA-A2-restricted CD8+ T-cell epitopes in chronic infection were significantly less frequently recognized during primary infection. This epitope was only recognized in chronic infection, and even then was recognized infrequently.

**HXB2 Location** Nef (180–189)

**Author Location** Nef (180–189 HXB2)

**Epitope** VLEWRFDSSL

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** Viet Nam

**Assay type** HLA binding

**Keywords** subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01\_AE variant IMwKfdsAl had a higher HLA-binding score than the HXB2 epitope, which isn't predicted to bind to A2.

**HXB2 Location** Nef (180–189)

**Author Location** Nef

**Epitope** VLEWRFDSSL

**Epitope name** A2-VL10(Nef)

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (180–194)

**Author Location** Nef (180–194)

**Epitope** VLVWKFDSRLAFRHM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The peptide VLvWKFDSRLAFrHM is a variant at positions 3 and 13, of consensus peptide LEWKFDSRLAFHHMA.

**HXB2 Location** Nef (180–194)

**Author Location** Nef (180–194)

**Epitope** VLMWKFDSRLAFHHI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing

Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.

- This epitope, VLMWKFDSRLAFHHI, varies at position 3 (methionine) from the consensus peptide LEWKFDSRLAFHHMA.

**HXB2 Location** Nef (181–189)

**Author Location** Nef (181–189)

**Epitope** LEWRFDSSL

**Epitope name** Nef181-189

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, immunodominance, characterizing CD8+ T cells

**References** Chandwani *et al.* 2004

- Responses to five HLA-A2 presented epitopes in Nef were characterized in a population of 19 HIV infected adults and 21 children. The CD8 T-cell response to Nef was stronger and broader in adults than children, averaging 652 and 87 SFCs/10<sup>6</sup> PBMC, and 2.6 and 0.9 recognized epitopes per person, respectively.
- This was not the immunodominant response.

**HXB2 Location** Nef (181–189)

**Author Location** Nef (180–)

**Epitope** LKWKFDSSL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2, Cw\*0602)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian subclade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope, LKWKFDSSL, is predicted to bind HLAs A2 and Cw\*0602 with binding affinities of 572.969 and 6 respectively.

**HXB2 Location** Nef (181–189)

**Author Location** Nef (183–)

**Epitope** LMWKFDSRL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope, LMWKFDSSLRL, is predicted to bind 70% of them with high affinity.

**HXB2 Location** Nef (181–195)

**Author Location** Nef

**Epitope** LEWKFDSSLAFHHMA

**Epitope name** nef-5184

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNPs by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, LEWKFDSSLAFHHMA was mutated in the daughter D2 isolate to LEWKFDSSLAFHHIA.

**HXB2 Location** Nef (181–195)

**Author Location** Nef (181–195)

**Epitope** LVWKFDSLLAFHHRA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, LvWKFDSsLAFHHrA, varies at positions 2, 8 and 14 from the consensus peptide LEWKFDSSLAFHHMA.

**HXB2 Location** Nef (181–195)

**Author Location** Nef (181–195)

**Epitope** LVWKFDSHLAFHHMA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, LvWKFDSHsLAFHHMA, varies at positions 2 and 8 from the consensus peptide LEWKFDSSLAFHHMA.

**HXB2 Location** Nef (182–189)

**Author Location** Nef (182–189)

**Epitope** EWRFDSSL

**Epitope name** EL8

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*08)

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.

- 2 PTE-B peptides, DPEREVLEWrFDSRL and VLvWKFD-SRLAFrHM contained the epitope EWRFSRL (EL8) and elicited IFN-gamma immune responses.

**HXB2 Location** Nef (182–189)

**Author Location** Nef (182–189)

**Epitope** EWRFSRL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21

**Species (MHC)** human (B8)

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization

**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of the 31 epitopes that the vaccinated volunteers responded to.

**HXB2 Location** Nef (182–196)

**Author Location** Nef (182–196)

**Epitope** VWRFDSLAFrHMAR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, VWrFDSLAFrHMAR, varies at positions 3, 7 and 11 from the consensus peptide LEWKFDLSRLAFHHMA.

**HXB2 Location** Nef (182–198)

**Author Location** Nef (182–198 BRU)

**Epitope** EWRFSRLAFHHVAREL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1, B8)

**References** Hadida *et al.* 1992

- HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients.

**HXB2 Location** Nef (182–198)

**Author Location** Nef (182–198 LAI)

**Epitope** EWRFSRLAFHHVAREL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2, A25)

**References** Hadida *et al.* 1995

- The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions.

**HXB2 Location** Nef (182–198)

**Author Location** Nef (182–198 BRU)

**Epitope** EWRFSRLAFHHVAREL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A25)

**References** Cheynier *et al.* 1992

- CTL isolated in children born to HIV-1 positive mothers.

**HXB2 Location** Nef (182–198)

**Author Location** Nef (182–198 LAI)

**Epitope** EWRFSRLAFHHVAREL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Hadida *et al.* 1995

- The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions.

**HXB2 Location** Nef (182–198)

**Author Location** Nef (182–198 LAI)

**Epitope** EWRFSRLAFHHVAREL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vaccinia, Mengo virus *Strain:* B clade LAI *HIV component:* Nef

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Van der Ryst *et al.* 1998

- Macaca mulatta did not have a detectable response to Rec Mengo virus-HIV-1 Nef 65-206 vaccine.
- BALB/c mice had a weak response to this epitope in the Mengo virus construct – in contrast, HIV-1 Nef induces a strong CTL response in mice when presented in a vaccinia background.

**HXB2 Location** Nef (182–201)

**Author Location** Nef (191–205 SF2)

**Epitope** EWRFSRLAFHHVARELHPE

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lieberman *et al.* 1997a

- Of 25 patients, most had CTL specific for more than 1 HIV-1 protein.
- Eleven subjects had CTL that could recognize vaccinia-expressed LAI Nef.
- One of these 11 had CTL response to this peptide.
- The responding subject was HLA-A2, B21.

**HXB2 Location** Nef (182–205)



**Author Location** Nef (182–205 LAI)

**Epitope** EWRFD SRLAFHHVARELHPEYFKN

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide

**Species (MHC)** human

**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long amino acid peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 4/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL response to at least one of the six peptides; each of the six peptides elicited a CTL response in at least one individual.
- None of the 12 tested had an IgG response to this peptide.

**HXB2 Location** Nef (183–191)

**Author Location** Nef (183–191)

**Epitope** WRFDSRLAF

**Epitope name** WF9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*15)

**Country** United States

**Assay type** Intracellular cytokine staining, Other

**Keywords** rate of progression, escape, immune evasion

**References** Karlsson *et al.* 2007

- To correlate evolving HIV-1 populations with HLA-A2 restricted immune responses for epitopes in Gag, Pol, Env and Nef, 11 treatment-naïve subjects were longitudinally studied. Results show that increased viral load is often associated with broad CTL responses early in infection that persist as an "immunological footprint". Conversely, early, restricted responses may help limit viral load. Phylogenetic and functional evidence of viral escape is seen in Gag, Nef and Pol. Gag and Nef show flanking epitope changes restricted by non-HLA-A2 alleles. As far as modes of viral adaptation, CTL responses were seen to develop both against static viral populations resulting in viral evolution to HLA-A2 as well as against existing mutants resulting in reselection of consensus B-like variants. This study reinforces that CTL immune responses detected are not necessarily beneficial to patients, but may be "footprints" from early effective responses that the virus has since escaped.
- No CTL responses were detected against the WF9 epitope, WRFDSRLAF. A 184K variant, WkFDSRLAF was found, that did elicit a potent HLA-B15 restricted immune response. Sporadic changes were seen in WF9 to WkFDSRLA (R185K).

**HXB2 Location** Nef (183–191)

**Author Location**

**Epitope** WRFDSRLAF

**Epitope name** Nef-WF9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Donor MHC** A\*2904, A\*3002, B\*1503, B\*5802, Cw\*0202, Cw\*0602

**Keywords** HAART, ART

**References** Sabbaj *et al.* 2003

- This study monitored epitope responses in HIV-1 infected minority women living in the United States.
- 24 epitopes were described – 8 were novel, 8 used new restricting elements but were previously defined epitopes, and 8 were previously described.
- Serial peptide truncations were used to define optimal epitopes for CTL cell lines isolated from 12 individuals, assayed by a Cr-release.
- This epitope was newly defined in this study.
- Subject 01RCH50 also recognized the epitope RMRGAHT-NDV, RT(356-365), A\*3002 – she was African American, was on HAART, had a viral load of 960 and CD4 count of 728.
- Among HIV+ individuals who carried HLA B15, 3/17 (18%) recognized this epitope.

**HXB2 Location** Nef (183–191)

**Author Location** Nef (183–191)

**Epitope** WRFDSRLAF

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Keywords** optimal epitope

**References** Frahm *et al.* 2008

**HXB2 Location** Nef (183–191)

**Author Location** Nef (183–191)

**Epitope** WRFDSRLAF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Donor MHC** A\*2301, B\*1503, B\*3501, Cw2, Cw7

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** binding affinity, acute/early infection, early-expressed proteins

**References** Cao *et al.* 2003

- All proteins were scanned and optimal epitopes were mapped in a study of CD8+ gamma IFN T-cell responses in 21 men within 15-92 days post-HIV-1 infection. Subjects initially showed narrow immune responses with a mean of 2.3 epitopes recognized per patient. The immune response broadened later in infection. No correlation between the plasma viral load and the number of recognized epitopes or the frequency of IFN-gamma secreting cells was observed, and there was no correlation between the functional avidity of a responses and the abundance of IFN-secreting cells that recognized the epitope. The first epitopes to be recognized did not tend to be the most avid, and earliest responses tended to be directed against Nef, Tat, Vpr, and Env.
- All HIV-1 proteins except Vpu were recognized, and a responses to a total of 41 optimal epitopes were characterized; 24 had been identified previously. 48% of the total T-cell responses were directed against Nef and 43% were directed against Gag.
- More common HLA alleles were less frequently used in primary infection than less common alleles, for example A3, B35, B57, and B62 were more frequently utilized than A1, A2, A30, and A44.

**HXB2 Location** Nef (183–191)  
**Author Location** Nef  
**Epitope** WRFDSRLAF  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Donor MHC** A\*0301, A\*2301, B\*0702, B\*1503  
**Country** United States  
**Keywords** escape, acute/early infection  
**References** Bernardin *et al.* 2005

- Full HIV genomes from nine individuals were analyzed for mutations prior to seroconversion and 7 to 28 days later. It was found that the influence of the host's HLA type was reflected within weeks of infection; a statistically significant number of early nonsynonymous mutations were observed within previously reported CTL epitopes.
- K to E mutation was observed in position 2.

**HXB2 Location** Nef (183–191)  
**Author Location** Nef (183–191)  
**Epitope** WKFDSRLAF  
**Epitope name** WF9  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** assay standardization/improvement, acute/early infection, immune evasion  
**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 5 additional variants of this epitope, WKFDSRLAF, were determined using PTE-B - WKFDSRLAI, WRFDSRLAF, WRFDSRLAF, WKFDSRLAF and WKFDSRLAF. The last 2 variants show reduced magnitude of response as compared to the consensus epitope while a variant WKFaSRLAF was the only patient autologous epitope sequence detected.

**HXB2 Location** Nef (183–191)  
**Author Location** Nef  
**Epitope** WKFDSRLAF  
**Subtype** B, C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (B\*1503)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, rate of progression, immunodominance  
**References** Frahm *et al.* 2006

- CTL responses restricted by HLA-B\*1503 were analyzed in HIV-1 subtype B and C-infected patients. An association between HLA-B\*1503 and reduced viral loads in individuals infected with clade B was found. No such correlation was found in clade C infected subjects in spite of the same immunodominant responses in subjects infected with either subtype. Clade

B viral control was associated with several subdominant CTL epitopes lacking in clade C, suggesting that subdominant responses can contribute to viral control.

- WKFDSRLAF of clade B is a potential HLA-B\*1503-restricted epitope, with epitope WKFDSRLAF found in clade C.

**HXB2 Location** Nef (183–191)  
**Author Location** Nef

**Epitope** WRFDSRLAF  
**Epitope name** B15-WF9(Nef)  
**Immunogen** HIV-1 infection

**Species (MHC)** human (B15)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, early-expressed proteins  
**References** Altfield *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (183–192)  
**Author Location** Nef (183–192)

**Epitope** WRFDSRLAFH  
**Subtype** B  
**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)  
**Donor MHC** A1, A3, B57, B7, Cw6, Cw7  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- This epitope was reactive, but escape mutations did not accrue in it over time.

**HXB2 Location** Nef (183–192)  
**Author Location** Nef

**Epitope** WRFDSRLAFH  
**Epitope name** A1-WH10(Nef)  
**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, immunodominance, early-expressed proteins

**References** Altfeld *et al.* 2006

- Immunodominant HIV epitopes in early, primary infection of CTLs were identified and the relative contribution of immune responses restricted to individual HLA class I molecules were studied.
- The most frequently recognised epitopes also elicited the greatest CTL response.
- HIV-1 Epitope sequence variability was not correlated with immunodominant versus immune sub-dominant responses.
- HLA-B57 and HLA-B27 restricted responses were the strongest in these early and acute infections - due to dominant responses to a single epitope in each case (TW10 for B57 and KK10 for B27).
- In the presence of HLA-B57 and HLA-B27 restricted responses, the relative contribution of other restricting HLA dropped greatly.

**HXB2 Location** Nef (183–197)

**Author Location** Nef (183–197)

**Epitope** WRFDSRLAFHHMARE

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B\*1503)

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, WRFDSRLAFHHMARE, varies at position 2 (arginine) from the consensus peptide LEWKFSRLAFHHMA.

**HXB2 Location** Nef (184–191)

**Author Location** Nef (184–191 HXB2)

**Epitope** RFDSRLAF

**Subtype** B, CRF01\_AE

**Immunogen** HIV-1 infection

**Species (MHC)** human (A1)

**Country** Viet Nam

**Assay type** HLA binding

**Keywords** subtype comparisons, computational epitope prediction, variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Lazaro *et al.* 2005

- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- CRF01\_AE common variant KfdaAlaR had same HLA-binding score as the HXB2 epitope.

**HXB2 Location** Nef (185–199)

**Author Location** Nef

**Epitope** FDSRLAFHHMARELH

**Epitope name** nef-5185

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)

**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism

**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains. Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.
- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, FDSRLAFHHMARELH was mutated in the daughter D2 isolate to FDSRLAFHHiAkELH.

**HXB2 Location** Nef (186–193)

**Author Location** Nef (186–193 LAI)

**Epitope** DSRLAFHH

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35)

**References** Hadida *et al.* 1995

- The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions.

**HXB2 Location** Nef (186–194)

**Author Location** Nef (186–194)

**Epitope** DSRLAFHHM**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human (A24)**Keywords** HIV exposed persistently seronegative (HEPS)**References** Kaul *et al.* 2001a

- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** Nef (186–194)**Author Location** Nef (186–194)**Epitope** DSRLAFHHM**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A24)**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B**Keywords** Th1, characterizing CD8+ T cells**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Two of seven patients responded to this peptide with GzB producing cells, while none of the patients responded with IFN-gamma producing cells.

**HXB2 Location** Nef (186–194)**Author Location** Nef (186–194)**Epitope** DSRLAFHHM**Epitope name** DM9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (A24)**Donor MHC** A\*24, A\*31, B\*15, B\*47, Cw\*04, Cw\*07; A\*24, A\*30, B\*39, B\*47, Cw\*12, Cw\*17; A\*23, A\*24, B\*07, B\*39, Cw\*12, Cw\*17**Country** United Kingdom**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** responses in children, mother-to-infant transmission, escape, acute/early infection, viral fitness and reversion**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in the infant over time was determined by infant HLA haplotype and viral fitness.
- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.

- DSRLAFHHM is a known A24 epitope. A known escape variant, DSRLAFqHM, was transmitted from an A24- mother to her A24+ infant, where it was gradually lost over time, present in 6/10 clones at 2 months, 7/10 at 4 months, and 0/10 at 15 months.

- Another escape variant was present in an A24+ mother, DStLAFqHk and this form was transmitted to her A24+ infant where it persisted in 30/30 sequences sampled over 12 months.
- DSRLAFHHM had higher responder cell frequencies in the A24+ mother than DStLAFqHk. Her A24+ infant did not recognize either form. The variant DSRLAFqHM also stimulated lower responder cell frequencies.

**HXB2 Location** Nef (186–194)**Author Location** Nef (186–194 BRU)**Epitope** DSRLAFHHV**Immunogen****Species (MHC)** human (B51)**References** Connan *et al.* 1994

- Resulted in the assembly of HLA-B51.

**HXB2 Location** Nef (186–194)**Author Location** Nef (186–194)**Epitope** DSRLAFHHV**Immunogen** HIV-1 infection**Species (MHC)** human (B51)**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8**Country** Netherlands**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** rate of progression, escape**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. The dsLlaLRhM variant residues arose at early time points, and the dsrlaVhhv variant residue arose at intermediate time points.

**HXB2 Location** Nef (186–194)**Author Location** Nef**Epitope** DSRLAFHHV**Epitope name** DV9**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A28, A29, B14, B44, Cw8**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion**References** Allen *et al.* 2005a

- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
- An escape mutation at position 7, DSRLAFqHV, was found not to correspond to the most polymorphic residue in the epitope. This is a novel unmapped epitope.

**HXB2 Location** Nef (188–196)

**Author Location** Nef (192–200 SF2)

**Epitope** KLAFFHHMAR

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (A\*3303)

**Assay type** Chromium-release assay

**Keywords** binding affinity, computational epitope prediction

**References** Hossain *et al.* 2003

- HLA-A\*3303 is a common HLA allele in east and southeast Asia. Pol, Gag and Nef SF2 proteins were scanned for potential A\*3303 epitopes. 99 potential epitopes were synthesized, and 52/99 bound to A\*3303. Six of these served as peptide-targets for lysis by PBMC from infected individuals, and clones derived from 4 of these 6 could lyse HIV-vaccinia infected target cells, indicating proper processing.
- This epitope is one of the 2/6 peptides that could induce CTL responses in the PBMC of infected individuals, but was not properly processed in a vaccinia-HIV infected target cell.

**HXB2 Location** Nef (188–196)

**Author Location** Nef (188–196)

**Epitope** RLAFFHHVAR

**Immunogen** peptide-HLA interaction

**Species (MHC)** (A11, A3)

**Assay type** HLA binding

**Keywords** binding affinity, immunodominance

**References** Racape *et al.* 2006

- Interaction between purified HLA-A3 molecules and several dominant CD8 epitopes was characterized. Amplitude, stability, and kinetic parameters of the interaction between HLA-A3, peptides, and anti-HLA mAbs were tested.
- Epitopes tested bound strongly to HLA-A3 and formed very stable complexes.
- Gag epitope RLRPGGKKK and Nef epitope RLAFFHHVAR complexes with HLA-A3 were not recognized by the A11.1 mAb specific to HLA-A3 alleles. The proposed explanation was that Arg at position P1 of the peptide may push the  $\alpha 2$  helix residue and affect mAb recognition.

**HXB2 Location** Nef (188–196)

**Author Location** Nef (188–196 LAI)

**Epitope** RLAFFHHVAR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B52)

**References** Hadida *et al.* 1995

- The C-terminal region of Nef (182-205) contains multiple CTL epitopes with 5 distinct HLA restrictions.

**HXB2 Location** Nef (188–201)

**Author Location** Nef (188–201 LAI)

**Epitope** RLAFFHHVARELHPE

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (B35, Cw4)

**References** Buseyne *et al.* 1993a

- Vertical transmission of HIV ranges from 13% to 39%
- Primary assays showed that cytotoxic activity against at least one HIV protein was detected in 70% of infected children.
- Epitopes recognized in five children were mapped using synthetic peptides and secondary cultures.
- Patient EM13, who had a CTL response to three epitopes in Nef, was infected via blood transfusion after birth and went from CDC stage P2A to P2E during the study.

**HXB2 Location** Nef (188–202)

**Author Location** Nef (188–202)

**Epitope** SLAFHHRARELHPEY

**Subtype** B

**Immunogen** computer prediction, HIV-1 and GBV-C co-infection

**Species (MHC)** human

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- SLAFHHRARELHPEY is a previously unpublished epitope that varies from the consensus at position 7.

**HXB2 Location** Nef (188–202)

**Author Location** Nef (188–202)

**Epitope** SLAFHHRARELHPEY

**Subtype** B

**Immunogen** computer prediction, HIV-1 and GBV-C co-infection

**Species (MHC)** human

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- SLAFHHrARELHPEY is a previously unpublished epitope, that varies from the consensus at the seventh position, arginine.

**HXB2 Location** Nef (189–198)  
**Author Location** Nef (189–198)  
**Epitope** LAFHHVAREL  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*6901)  
**Country** India  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, immunodominance  
**References** Thakar *et al.* 2005

- PBMCs from HIV-1 infected Indian subjects were tested for HIV-1 Gag (with C clade peptides), Nef (with B clade peptides), and Env (clade unspecified) specific T-cell responses. 5 immunodominant regions conserved across clades were identified in Gag and Nef. 3 antigenic regions were found to be recognized by CTLs in the Indian subjects; these regions were not identified as immunodominant in studies from Africa. 26 epitopes were predicted within reactive peptides, of which 90% were clustered in the conserved immunodominant regions of Gag and Nef. 3 of the epitopes were highly conserved across clades, and 7 novel epitopes were found.

**HXB2 Location** Nef (189–203)  
**Author Location** Nef  
**Epitope** LAFHHMARELHPEYY  
**Epitope name** nef-5186  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201, A\*19, B\*3501, B\*44, Cw\*07, Cw\*16)  
**Donor MHC** A\*01, A\*19, B\*14, B\*44, Cw\*08, Cw\*16  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** HAART, ART, mother-to-infant transmission, rate of progression, co-receptor, immune evasion, HLA associated polymorphism  
**References** Reinis *et al.* 2007

- HIV-1 mother-to-child transmission is studied for LTNP by comparing entire genomes from 2 mother (M1, M2) and 2 daughter (D1, D2) RNA samples of a mother-child pair over 11 years. Genetic distance was 94% between subjects' strains.

Divergence in sequences was attributed to distinct HLA selection pressures as ds/dn was larger for intra- rather than inter-person sequences. 10 new mutations in D2 were found related to unique daughter HLA alleles.

- Functional ELISpot studies using D2 and Nef peptides reveal strong associations between CTL responses and escape variants, contributing to delayed progression.
- LTNP status was not related to defective virus since all viral genes were intact and CTL response did not effectively control viral load. It is supposed that genetic HLA background and HIV-1 epitope-immune response interaction account for nonprogression of disease.
- All isolates contained R77Q in Vpr, a variation associated with reduction of cellular apoptosis.
- This Nef overlapping peptide, LAFHHMARELHPEYY was mutated in the daughter D2 isolate to LAFHHMAKELHPEYY.

**HXB2 Location** Nef (190–198)  
**Author Location** Nef  
**Epitope** AFHHVAREL  
**Epitope name** Nef AL9  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*0201)  
**Keywords** subtype comparisons, supertype, computational epitope prediction  
**References** Altfield *et al.* 2001c

- HIV was scanned for all peptides which carried the A2-supermotif pattern conserved in more than 50% of B clade sequences – 233 peptides met this criteria, and 30 of these bound to HLA-A\*0201 – 20/30 bound to at least 3/5 of HLA-A2 supertype alleles tested.
- Three additional previously described HLA-A2 epitopes were added to the set of 20, including Nef AL9, and 18/22 chronically infected HLA-A2 individuals had CTL that recognized at least one of the 23 peptides (median of 2 and maximum of 6), while 6/12 acute infected individuals recognized at least 1 (median of 1 and maximum of 2)
- RT VL9 was not recognized by any of the 22 HLA-A2 patients with chronic HIV-1 infection or the 13 HLA-A2 patients with acute HIV-1 infection included in this study.

**HXB2 Location** Nef (190–198)  
**Author Location** Nef  
**Epitope** ALKHRAYEL  
**Subtype** A  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade HIV component: p17 Gag, p24 Gag  
**Species (MHC)** human, macaque (A\*0201)  
**Keywords** subtype comparisons, epitope processing, immunodominance  
**References** Hanke & McMichael 2000; Wee *et al.* 2002

- The HIV-1 subtype A focused vaccine HIVA contains p24 and p17, in a reversed order relative to the Gag polyprotein to prevent myristylation of p17, which could direct the protein to the cell membrane and inhibit efficient peptide processing and class I presentation, as well as a polypeptide string of conserved, often immunodominant epitopes that were selected to

have particularly good cross-reactive potential for the A-clade epidemic in Nairobi, Kenya. A DNA and MVA prime-boost vaccination protocol using the HIVA antigen will be used in a phase III clinical trial in Kenya. This epitope is included in the polyepitope string Hanke & McMichael [2000].

- Multiple CD4+ or CD8+ T-cell vaccine-induced responses to peptide pools were detected using intracellular cytokine staining and IFN $\gamma$  ELISPOT assays after vaccination of 5 macaques. The response to the Mamu A\*01 SIV p27 epitope p11C (CTPYDINQM), included in the polyepitope region, was not immunodominant in the Mamu A\*01 vaccinated macaques, possibly because of processing limitations in context of the artificial polyepitope string Wee *et al.* [2002].

**HXB2 Location** Nef (190–198)

**Author Location** Nef (190–198 LAI)

**Epitope** AFHHVAREL

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human (A2)

**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)

**References** Rowland-Jones *et al.* 1998a

- CTL recognition reported in the context of HLA-B52 and A2.1, A2.2 and A2.4.
- A CTL response was found in exposed but uninfected prostitutes from Nairobi using previously-defined B clade epitopes that tended to be conserved in A and D clades – such cross-reactivity could protect against both A and D and confer protection in Nairobi where both subtypes are circulating.
- The A subtype consensus is ALKHRAYEL.
- The D subtype consensus is AfEHKAREM.
- Hunziker *et al.* [1998] suggests that HLA-A2 does not in fact present this epitope, and notes that it does not promote A2 assembly Connan *et al.* [1994] – also see Brander *et al.* [1998b]
- Hunziker *et al.* [1998] maintains that HLA-A2 does not present this epitope contrary to an earlier report Hadida *et al.* [1995], (also see Brander *et al.* [1998a])—despite the position of Hunziker *et al.*, Rowland-Jones and colleagues are confident that this epitope in its A clade form is presented by HLA-A\*0201 and A\*0202, and it is one of the most common responses seen in both seropositive and exposed-uninfected donors from Nairobi (Rupert Kaul, pers. comm.)

**HXB2 Location** Nef (190–198)

**Author Location** Nef (190–198)

**Epitope** AFHHVAREL

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (A2)

**Keywords** binding affinity, dendritic cells, Th1

**References** Wilson *et al.* 1999b

- Dendritic cells are the most potent for priming T cell responses – DCs can stimulate autologous CTL responses from T cells cultured from HIV negative donors.
- Th1-biasing cytokines IL-12 or IFN alpha enhance CTL responses *in vitro* whether the epitope is delivered by pulsing from peptide, or expressed from within.

- B7 and A2 Nef epitopes were studied and the relative binding affinity of A2 epitopes for A2 was: PLTFGWCYKL greater than VLEWRFDSSL which was much greater than AFHHVAREL.

**HXB2 Location** Nef (190–198)

**Author Location** Nef (190–198)

**Epitope** AFHHVAREL

**Immunogen** vaccine

*Vector/Type:* vaccinia

**Species (MHC)** human (A2)

**References** Woodberry *et al.* 1999

- A polyepitope vaccine was generated in a vaccinia construct that contiguously encoded seven epitopes, all presented by HLA A-2.
- HHD mice have a transgene of HLA A2 linked to the transmembrane and cytotoxic domains of H-2D<sup>d</sup> – this transgene is the only MHC molecule expressed in the mice.
- CTL responses to Gag (77-85) SLYNTVATL, Pol (476-484) ILKEPVHGV, gp120 (120-128) KLTPLCVTL, and Nef (190-198) AFHHVAREL were observed in HIV polytope HHD-vaccinated mice, and these responses were enhanced with vaccinia boost.
- No CTL immune responses were generated against HLA A2-restricted HIV epitopes Nef 157-166 (PLTFGWCYKL), Pol 346-354 (VIYQYMDDL), and Nef 180-189 (VLEWRFDSSL)
- Sixteen HLA A2+ patients were tested for their ability to make CTL responses by peptide restimulation in culture with the epitopes selected for inclusion in the polytope – one individual recognized all seven of these epitopes; 7 patients had CTL cultures able to recognize at least one of the epitopes, and 6 of those 7 recognized more than one epitope, but they were not able to test all peptides for all patients; many patients only had three peptides tested.
- AFHHVAREL was recognized by 2 of the patients.

**HXB2 Location** Nef (190–198)

**Author Location** Nef (190–198 SF2)

**Epitope** AFHHVAREL

**Immunogen** HIV-1 infection

**Species (MHC)** human (A2)

**Keywords** HAART, ART, acute/early infection

**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.
- The breadth and specificity of the response was determined using ELISPOT by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Previously described and newly defined optimal epitopes were tested for CTL response.
- Number of HLA-A2+ individuals that had a CTL response to this epitope broken down by group: 0/10 group 1, 1/6 group 2, and 0/4 group 3.

**HXB2 Location** Nef (190–198)  
**Author Location** Nef (190–198)  
**Epitope** ALKHRAYEL  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human (A2)  
**Keywords** subtype comparisons, HIV exposed persistently seronegative (HEPS)  
**References** Kaul *et al.* 2001a

- Variants ALKHRAYEL and AFHHVAREL are A/B clade specific.
- ELISPOT was used to study CTL responses to a panel of 54 predefined HIV-1 epitopes in 91 HIV-1-exposed, persistently seronegative (HEPS) and 87 HIV-1-infected female Nairobi sex workers.

**HXB2 Location** Nef (190–198)  
**Author Location** Nef (190–)  
**Epitope** AFHHVAREL  
**Epitope name** Nef190  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2)  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay  
**Keywords** binding affinity, subtype comparisons, computational epitope prediction  
**References** Corbet *et al.* 2003

- HLA-A2-restricted HIV-1 CTL epitopes were computationally predicted. Binding affinities for HLA-A\*0204, immunogenicity in HLA-A\*0201 transgenic mice, and responses to the peptides in 17 HIV-1 infected patients were tested. 31 novel conserved A2 epitopes were detected. An average of 4 epitopes were recognized per patient.
- This epitope was one of the previously identified HLA-A2 epitopes studied.
- None of the 17 HIV-infected HLA-A2+ people in this study recognized this epitope.

**HXB2 Location** Nef (190–198)  
**Author Location** Nef (190–198)  
**Epitope** ALHHVAREL  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21  
**Species (MHC)** human (A2)  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** vaccine-induced epitopes  
**References** Gahéry-Ségard *et al.* 2003

- After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that the vaccinated volunteers responded to.

**HXB2 Location** Nef (190–198)  
**Author Location** Nef (subtype B)  
**Epitope** AFHHVAREL  
**Subtype** B  
**Immunogen** HIV-1 exposed seronegative  
**Species (MHC)** human (A\*0201, A\*0202, A2)  
**Keywords** subtype comparisons  
**References** Rowland-Jones *et al.* 1998b

- HIV-specific CTL were found in exposed seronegative prostitutes from Nairobi – these CTL may confer protection.
- Seroprevalence in this cohort is 90-95% and their HIV-1 exposure is among the highest in the world.
- Most isolated HIV strains are clade A in Nairobi, although clades C and D are also found – B clade epitopes are often cross-reactive, however stronger responses are frequently observed using A or D clade versions of epitopes.
- Clade A version of the epitope: ALKHRAYEL, Clade D epitope: AFEHKAREM.
- This epitope was recognized by two different exposed and uninfected prostitutes.

**HXB2 Location** Nef (190–198)  
**Author Location** Nef (190–198)  
**Epitope** AFHHVAREL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A2, B52)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell Elispot granzyme B  
**Keywords** Th1, characterizing CD8+ T cells  
**References** Kleen *et al.* 2004

- Only 20% of CD8+ T-cells produce IFN-gamma and granzyme B simultaneously (Tc1a). Two additional subpopulations of HIV specific CD8 cells are found, each one constituting 30-40% of the CD8 cell pool. One of these (Tc1b) secretes IFN-gamma only, and the other one (Tc1c) secretes GzB only.
- Three of seven patients responded to this peptide with GzB producing cells, while one of three patients also responded with IFN-gamma producing cells.

**HXB2 Location** Nef (190–198)  
**Author Location** Nef (190–198 HXB2)  
**Epitope** AFHHVAREL  
**Subtype** B, CRF01\_AE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A24)  
**Country** Viet Nam  
**Assay type** HLA binding  
**Keywords** subtype comparisons, computational epitope prediction, escape, variant cross-recognition or cross-neutralization, vaccine antigen design  
**References** Lazaro *et al.* 2005



- The most common HLA-alleles in the Vietnamese population were found to be HLA-A11, A02, A33, B75, B46, and B62. Several epitopes cluster in short regions in Gag and Nef that are presented by these HLA molecules; these epitopes may be useful targets for vaccine antigens. In a comparison of CRF01\_AE sequences to HXB2, 14 mutations were found in epitopes in these Gag and Nef pluriepitopic regions; 7 did not affect the HLA binding score, 3 increased it, and 4 reduced it.
- ArrHiAREL, ArtHiAREL, and ArkHiAREL variants are the three forms found in CRF01, and none are predicted to bind to A24.

**HXB2 Location** Nef (190–198)

**Author Location** Nef (190–198 LAI)

**Epitope** AFHHVAREK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**References** Hadida *et al.* 1995

- Naturally occurring L to K anchor substitution abrogates A2 binding, but permits HLA-A3 binding.

**HXB2 Location** Nef (190–198)

**Author Location** Nef (190–198)

**Epitope** AFHHVAREK

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Country** Spain

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** HAART, ART, supervised treatment interruptions (STI), immune dysfunction

**References** Plana *et al.* 2004

- Structured treatment interruption (STI) alone is not able to control viral replication in chronically infected patients, probably due to lack of strong, maintained T-helper cell responses. HIV-1 specific CD8+ T-cell responses were shown to increase significantly until the end of the follow up, but were not correlated with viral load.
- Less than 2 of 14 patients recognized this epitope.

**HXB2 Location** Nef (190–198)

**Author Location** Nef (190–198)

**Epitope** AFHHVAREK

**Epitope name** AL9

**Immunogen** HIV-1 infection

**Species (MHC)** human (A3)

**Donor MHC** A\*03, A\*31, B\*08, B\*15, Cw\*04, Cw\*07

**Country** United Kingdom

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children, mother-to-infant transmission, escape, characterizing CD8+ T cells, viral fitness and reversion

**References** Sanchez-Merino *et al.* 2005

- CD8 T-cell responses were examined in mother-infant pairs. Escape variants were commonly detected in maternal plasma. Early infant plasma viruses showed heterogeneity of gag and nef gene sequences as well as mother-to-child transmission of CD8 T-cell escape variants. The stability of escape mutants in

the infant over time was determined by infant HLA haplotype and viral fitness.

- Sequential plasma specimens from infants showed changes in CD8 T-cell epitope sequences, suggesting that infants are capable of generating virus-specific CD8 T-cell responses.
- AFHHVAREK is an A3 epitope, and a mixture of variants was present in the mother and in her A3- (A31+) infant at 2 months. One of the variants was AFqHmAREL, and this form was not found in 10 clones at the 15 month time point.

**HXB2 Location** Nef (190–198)

**Author Location** Nef (190–198)

**Epitope** AFHHVAREK

**Immunogen** HIV-1 infection

**Species (MHC)** human (B51)

**Donor MHC** A03, A32, B15, B51, Cw03, Cw06, DQ7, DR4, DR8

**Country** Netherlands

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** rate of progression, escape

**References** Geels *et al.* 2003

- Both stable potential epitopes and epitopes with escape mutations were found in a patient with increasing viral load over a time period of 4 years. Fixation of escape mutations occurred sequentially and correlated with the rise in viral load and with the increased number of productively infected cells.
- This is one of 7 epitopes from this individual that varied over time, although the internal mutations did not become fixed. The aLRhMarek variant residues arose at early time points, the aVhhvarek variant residue arose at intermediate time points, and afhhvaXeI variant residues arose at late time points.

**HXB2 Location** Nef (190–198)

**Author Location** Nef (189–)

**Epitope** AHRHMAREL

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human (Cw\*0602)

**Country** India

**Assay type** Other

**Keywords** subtype comparisons

**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope AHRHMAREL, is predicted to bind HLA-Cw\*0602 with a binding affinity score of 6.6.

**HXB2 Location** Nef (190–198)

**Author Location**

**Epitope** ALKHRAYEL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Kaul *et al.* 2001c

- This study examines CTL responses in HIV exposed, persistently seronegative individuals, HEPS, who eventually seroconverted – 11/114 HEPS Nairobi sex workers eventually seroconverted, and for six of these HIV CTL reactive epitopes had been defined while seronegative.
- The epidemiological factor associated with seroconversion was stopping sex work. HIV-specific CTL activity declined when HEPS sex workers stopped working for a period or retired.
- This epitope was in 1/22 HEPS controls, ML1749.

**HXB2 Location** Nef (190–198)

**Author Location** Nef (190–198)

**Epitope** AFHHVAREL

**Epitope name** AL9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** assay standardization/improvement, acute/early infection, immune evasion

**References** Malhotra *et al.* 2007a

- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
- 2 PTE-B peptides, KFDSRLAFHHVAREL and KFSRLAFH-HiAREkH contained the epitope AFHHvAREL (AL9) and elicited IFN-gamma immune responses.

**HXB2 Location** Nef (190–204)

**Author Location** Nef (190–204)

**Epitope** AFRHVARELHPEYFK

**Subtype** B

**Immunogen** computer prediction, HIV-1 and GBV-C co-infection

**Species (MHC)** human (A3)

**Donor MHC** A24, A3, B7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This epitope, AFRHvARELHPEYfK, is a variant of the consensus peptide at positions 3, 5 and 14.

**HXB2 Location** Nef (190–204)

**Author Location** Nef (190–204)

**Epitope** AFHHMARELHPEYYK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- The unpublished epitope AFHHMARELHPEYYK is a variant of the consensus peptide LAFHHMARELHPEYY.

**HXB2 Location** Nef (190–204)

**Author Location** Nef (190–204)

**Epitope** AFRHVARELHPEYFK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** B\*1503, B35, B7 supertype, Cw7

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** computational epitope prediction, vaccine-induced epitopes

**References** Li *et al.* 2006b

- To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
- This peptide, AFRHvARELHPEYfK, varies at positions 3 and 5 from the consensus peptide HMARELHPEYYKDC.

**HXB2 Location** Nef (190–206)

**Author Location** Nef

**Epitope** AFRHMARELHPEYYKNC

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A1, A3, B57, B7, Cw6, Cw7

**Country** United States

- Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, escape, characterizing CD8+ T cells, viral fitness and reversion  
**References** Allen *et al.* 2005a
- Two-thirds of all mutations arising in non-envelope proteins during the transition from acute to chronic infection were found to be due to either CD8 T-cell-associated selective pressures or reversion of HLA-I-associated mutations selected in a previous host. The predominance of escape mutations at highly polymorphic sites was observed across different HIV-1 clades.
  - Novel unmapped epitope.
  - AFRHMARELHPEYYKNC acquired a substitution over time, AFRHMAREmHPEYYKNC.
- HXB2 Location** Nef (191–205)  
**Author Location** Nef (191–205)  
**Epitope** FHHKARELHPEYYKD  
**Subtype** B  
**Immunogen** computer prediction, HIV-1 and GBV-C co-infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** computational epitope prediction, vaccine-induced epitopes  
**References** Li *et al.* 2006b
  - To assess the efficiency of vaccine-elicited T-cell responses to epitopes in circulating strains of HIV-1 rather than to consensus or ancestor epitope sequences, the authors used potential T-cell epitopes (PTEs) from Gag, Pol, Nef and Env proteins, to construct an epitope prediction model for peptide selection. Evaluation in their method was conducted by testing Nef-specific CTL responses in four HIV-1 subtype B infected subjects. It was found that peptides autologous to HIV-1 immunogen sequence were the best for vaccine design and that vaccine response evaluation was better performed using peptide sets from circulating strains of HIV-1.
  - This peptide FHHKARELHPEYYKD, varies from the consensus at the fourth position, lysine.

**HXB2 Location** Nef (192–206)  
**Author Location** Nef (192–206 BRU)  
**Epitope** HHVARELHPEYFKNC  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A1)  
**References** Hadida *et al.* 1992
  - HIV-1 specific CTLs detected in lymphoid organs of HIV-1 infected patients.

**HXB2 Location** Nef (195–202)  
**Author Location** Nef (195–202)  
**Epitope** ARELHPEY  
**Epitope name** AY8  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A\*01)  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other  
**Keywords** assay standardization/improvement, acute/early infection, immune evasion

- References** Malhotra *et al.* 2007a
- The ability of T cells from early infected subjects to recognize Nef clade B HIV-1 epitope variants was tested using both a consensus peptide panel and a standardized potential T-cell epitope panel (PTE-B). The magnitude and breadth of PTE-optimized peptide panels was significantly higher than CON peptides'. 29 potential epitopic domains were detected in Nef using the PTE peptide set.
  - A PTE-B peptide, FHHKARELHPEYYKD contained the epitope ARELHPEY (AY8) and elicited a IFN-gamma immune response.
- HXB2 Location** Nef (195–202)  
**Author Location** Nef (195–202)  
**Epitope** ARELHPEY  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Env, Gag, Nef *Adjuvant:* QS21  
**Species (MHC)** human (A1)  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization  
**References** Gahéry-Ségard *et al.* 2003
  - After injection of an anti-HIV-1 lipopeptide vaccine and the booster injections, a response was observed in >85% of 28 volunteers, and a long-term immune response was observed in >50% of the volunteers. A positive effect of QS21 adjuvant was found for B- and CD4+T-cell responses. A higher number of CD8+ T-cell epitopes was induced after a fourth boost injection. This epitope was one of 31 that were recognized in the vaccinees.

**HXB2 Location** Nef (195–202)  
**Author Location** Nef (195–202 BRU)  
**Epitope** ARELHPEY  
**Subtype** B, CRF02\_AG  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (A1)  
**Country** Cote D'Ivoire  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons  
**References** Inwoley *et al.* 2005
  - CD8+ T-cells from HIV-1 CRF02\_AG-infected Ivorians could recognize clade B epitopes. No difference was observed in the number of recognized peptide pools between nine French subtype B infected study subjects, and nine CRF02\_AG infected Ivorian subjects.
  - This epitope was recognized by 0/9 CRF02\_AG-infected patients, and by 1/9 B-infected patients. Sequence variants with two amino acid substitutions were found in 5/6 Ivorian subjects.
  - An epitope variant was found in 1/4 French patients, and it happened to be the one patient that recognized the epitope: AREmHPEY.

**HXB2 Location** Nef (195–203)  
**Author Location** Nef (194–)

**Epitope** ARELHPEFY**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human (B\*2702, B\*2705)**Country** India**Assay type** Other**Keywords** subtype comparisons**References** Kumar *et al.* 2006a

- Comparative sequencing and phylogenetic analyses of nef genes from 43 Indian AIDS patients showed a majority of HIV-1 subtype C viruses, forming a distinct Indian sub-clade. Potential epitopes were computationally predicted within these Nef proteins.
- Of the most common HLA in India tested, this epitope ARELHPEFY, is predicted to bind HLAs - B\*2702 and B\*2705 with binding affinity scores of 200 and 1000.

**HXB2 Location** Nef**Author Location** Nef**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human (A\*0201, Cw\*08)**References** Shacklett *et al.* 2000

- HIV-1 specific, MHC class I-restricted CTL killing was detected in duodenal and rectal gut associated lymphoid tissue (GALT) sites from three infected individuals – the distribution of class I restricted CTL was different in the peripheral blood samples and GALT samples.

**HXB2 Location** Nef**Author Location** Nef**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (B\*35)**Keywords** rate of progression**References** Jin *et al.* 2002

- Patients with HLA-B\*35 variants B\*3502, B\*3503, B\*3504, and B\*5301 tend to proceed to AIDS more quickly than those with B\*3501.
- Of 32 patients with HLA-B\*35 alleles CD8+ CTL responses were quantified using an intracellular cytokine staining assay – 75% had responses to Pol, 69% to Gag, 50% to Nef, and 41% to Env.
- The overall magnitude of CTL responses did not differ between those bearing B\*3501 and the others. A higher percentage of Gag responses was observed in those that had lower RNA levels that carried B\*3501, and there was a negative association with viral load and CTL activity. The data is consistent with higher levels of CTL responses contributing to protection in B\*3501 individuals, but not in B\*3502, B\*3503, B\*3504, and B\*5301 individuals.

**HXB2 Location** Nef**Author Location** Nef**Epitope****Subtype** B**Immunogen** vaccine**Vector/Type:** DNA **Strain:** B clade NL43**HIV component:** Nef **Adjuvant:** Bupivacaine**Species (MHC)** mouse (H-2<sup>d</sup>)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ **Keywords** class I down-regulation by Nef, vaccine antigen design**References** Majumder *et al.* 2003

- Non-functional Nef vaccine constructs that do not down-regulate class I or CD4 proteins are shown to be capable of inducing primary and memory T cell immune response after DNA vaccination in BALB/c mice, which makes them good candidates for vaccines.
- The responses to peptide pools suggest the C-terminal region of Nef is more immunogenic (the two most reactive peptide pools spanned positions 126-175, and positions 166-215).

**HXB2 Location** Nef**Author Location** Nef (BRU)**Epitope****Immunogen** vaccine**Vector/Type:** DNA **Strain:** B clade BRU**HIV component:** Nef**Species (MHC)** mouse (H-2D<sup>d</sup>)**References** Collings *et al.* 1999

- A comparison of DNA vaccination with HIV-1 Nef expression vectors pBN-CMV-NEF and pBN-RSV-NEF (self-replicating), pCGE2-NEF (non-replicating).
- CTL immune responses were detected using all three expression vectors, while a humoral immune response to Nef was only observed in the self-replicating expression vectors; possibly antibody responses require higher levels of protein expression.

**HXB2 Location** Nef**Author Location** Nef (SIV)**Epitope****Immunogen** SIV infection**Species (MHC)** macaque (Mamu-A\*11, Mamu-B\*03, Mamu-B\*04, Mamu-B\*17)**References** Dzuris *et al.* 2000

- Cell binding assays for Mamu molecules were employed to describe the peptide binding motifs for Mamu-A\*11, -B\*03, -B\*04, and -B\*17 CTL epitopes – a similarity for Mamu-A\*11 and -B\*03 and human HLA-B\*44 and -B\*27, respectively, was observed – all epitopes studied were SIV epitopes, so not specifically listed here.

**HXB2 Location** Nef**Author Location** Nef (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** rate of progression, Th1**References** Wasik *et al.* 2000

- HIV+ infants that progressed rapidly to AIDS had lower Th1 responses and decreased production of beta-chemokines and IL-2 relative to other HIV+ infants.

- No HIV+ infants had no demonstrable CTL at birth, but Th1 responses accompanied by CTL responses developed in children with slowly progressive disease, and not in rapid progressors.
- CTLp frequencies were determined by limiting dilution using autologous B cells infected with vaccinia/HIV constructs.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** De Maria *et al.* 1997

- CD3+ cells that also carry a natural killer cell receptor (NKR+) can exhibit down regulation of T cell function.
- Anti-NKR IgM MAb masked this inhibitory function and increased HIV-1 specific CTL activity in phytohemagglutinin-activated PBMC cultured in the presence of IL-2 from 3/5 patients, and in one other case anti-NKR MAb brought HIV-1 specific CTL activity to detectable levels.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lubaki *et al.* 1999

- Three strategies were used to analyze CTL activity: area under the net HIV-specific lysis curve (ACU), linear regression (LR) of net specific lysis, and the standard method, lytic units (LU20)
- A correlation between low HIV plasma viral load and increased levels of HIV-specific Gag and Nef CTL activity was observed using ACU and LR, but not LU20.

**HXB2 Location** Nef

**Author Location** Nef (LAI)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade SF2  
*HIV component:* Env, Gag, Nef, Protease

**Species (MHC)** human

**References** Gorse *et al.* 1999b

- The vaccine used was rec canarypox expressing HIV-1 env, gag, pol, nef and protease (vCP300) with or without administration of HIV-1 SF-2 rgp120.
- In vitro inducible CTL activity against HIV-1 Env, Gag, Pol, and Nef antigens was observed in 79% (15 of 19) of vaccine recipients.
- The combination of vCP300 and vP1291 together resulted in an overall increase in CTL induction and detection sensitivity.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** TCR usage

**References** Gamberg *et al.* 1999

- 13/13 subjects with advanced HIV infections showed CD8 T cell proliferation and differentiation of CTL *in vitro*, and six individuals showed HIV-specific responses to Gag, Pol, Env or Nef antigens.
- Data suggests that the functional and genetic integrity of the CD8 T cell repertoire (TCR betaV gene intrafamily genetic diversity) remains intact through advanced HIV infection, although HIV-specific CTL activity decreases.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Nef, Rev, Tat

**Species (MHC)** human

**Keywords** HAART, ART

**References** Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN-gamma production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

**HXB2 Location** Nef

**Author Location** Nef (LAI)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Buseyne *et al.* 1998a

- This study showed a correlation between strong CTL memory and breadth of response in 7-12 month old infants, and remaining AIDS-free for the first year of life, higher absolute CD4 and CD8 cells, and lower viral load.

**HXB2 Location** Nef

**Author Location** Nef (LAI)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Buseyne *et al.* 1998b

- In infants with positive CTL responses, most responses showed cross-clade reactivity with somewhat diminished recognition of epitopes from different subtypes.

**HXB2 Location** Nef

**Author Location** Nef (LAI)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* canarypox *HIV component:*  
Gag, gp120, gp41, Nef, Protease, RT

**Species (MHC)** human

**References** Evans *et al.* 1999

- A Canarypox vaccine expressing gp120, gp41, Gag, Protease, Nef and Pol CTL epitopes gave rise to CTL that could be detected in 61% of the volunteers – responses to Gag, Env, Nef and Pol were detected 3-6 months after the last vaccination.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** da Silva & Hughes 1998

- CTL dense regions of Nef tend to lie in conserved domains with low non-synonymous substitution per site – authors consider that this may be due to a host adaptation to infection that focuses the CTL response to be directed against conserved functional domains da Silva & Hughes [1998]

**HXB2 Location** Nef

**Author Location** Nef (LAI)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Legrand *et al.* 1997

- Seventeen recently infected patients were tested for CTL response to HIV proteins Env, Gag, Pol, Rev, Nef, Vif and Tat.
- An early response (within a month following PI) was noted in 87% of the subjects to Gag, 75% to Env, and 50% to Nef.
- Early responses to Pol, Rev, Vif and Tat were rare.

**HXB2 Location** Nef

**Author Location** Nef (LAI)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression

**References** Zerhouni *et al.* 1997

- CTL responses to Env, Gag, Nef and RT were tested at various phases of disease progression – 10 asymptomatic patients generally had CTL responses to all proteins, 10 ARC patients responded well to all proteins except Nef, and AIDS patients had few responses to any proteins.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)**

**Keywords** epitope processing

**References** Kuiken *et al.* 1999

- A correlation between conserved regions of Nef and CTL epitope density was also noted in Kuiken *et al.* [1999]. The authors suggest that this may be due to biological reasons such as the one described above da Silva & Hughes [1998], or due to epitope processing, or may be an artifact of experimental strategy for epitope definition, such that conserved epitopes would tend to be identified because they are more likely to be cross-reactive with the test reagents.

- Both p17 and Nef show a correlation between epitope density and conserved regions in the protein; in contrast, p24 is a more conserved protein, and known epitopes are evenly distributed across p24.

**HXB2 Location** Nef

**Author Location** Nef (BRU)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression

**References** Aladdin *et al.* 1999

- In vitro measurements of CTL-activity by Cr release assay in bulk culture showed no correlation between CTL-activity (gp120, Gag, Pol and Nef) and disease progression as measured by viral load, CD4 and time to death.

**HXB2 Location** Nef

**Author Location** Nef (SF2)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Jin *et al.* 1998a

- CTL precursor frequencies were determined in HIV-1 infected pregnant women, and higher CTLp frequencies to Pol and SF2 Nef, but not IIIB Nef, were found in non-transmitting mothers than in transmitting mothers – Nef CTL responses have been found in uninfected infants born to HIV+ women (Lazuriaga95);

**HXB2 Location** Nef

**Author Location** (subtype C)

**Epitope**

**Subtype** C

**Immunogen**

**Species (MHC)** human

**Keywords** subtype comparisons, immunodominance

**References** Novitsky *et al.* 2001

- This study provides a survey of CTL responses and full length HIV-1 genome sequences from a C subtype infected Botswanan cohort.
- 37 of 45 subjects (82%) demonstrated Nef specific ELISPOT CTL responses of more than 100 SFC/106 PBMC.
- Two Nef-immunodominant regions were identified, one spanned amino acid positions 67 to 96 using HXB2 numbering system while the second corresponded to amino acid positions 122 to 141.
- While there was some subtype B and C cross-reactivity, there was greater breadth and intensity of response if the CTL from HIV-1-infected individuals was probed with ELISPOT using peptides derived from the same subtype (a median of three Nef epitopes recognized within subtype C compared with one Nef

epitope recognized from subtype B peptides, and ELISPOT results with a median of 763 SFC/106 PBMC among responses to HIV-1 C, versus a median of 318 SFC/106 PBMC among responses to HIV-1 B.

**HXB2 Location** Nef

**Author Location** Nef (subtype A, B, D)

**Epitope**

**Subtype** A, B, D

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Cao *et al.* 2000

- HIV-1 subtypes A and D dominate the Ugandan epidemic, and a vaccine trial using B clade antigen is underway – this study addresses relative levels of cross-reactive CTL responses in HIV infected Ugandans to A, D, and B clade recombinant vaccinia viruses expressing Gag, Env, Pol, RT or Nef from HIV-1 clades A, B, and D.
- Proteins corresponding to the subtype of the infecting strains tended to trigger higher levels of CTL response measured by percent specific lysis, but there was extensive inter-subtype cross-reactivity with B clade proteins and the co-circulating subtype.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)

**Species (MHC)** human

**Keywords** review

**References** Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on the stimulatory role of CpG motifs and how HIV-1 DNA vaccines can boost the CTL and Th proliferative responses in asymptomatic HIV+ individuals.

**HXB2 Location** Nef

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human

**Keywords** HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission

**References** De Maria *et al.* 1994; Kuhn *et al.* 2002

- 6/24 HIV uninfected infants (ages 15-50 months) born to HIV+ mothers had HIV-1 specific CTL responses to vaccinia-expressed Nef, Gag/Pol, Env.
- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** Nef

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, escape

**References** Yusim *et al.* 2002

- Epitopes that have been described in the literature and included in this database tend to cluster in conserved regions and be absent or rarely found in highly variable regions in Nef, Env, and p17.
- While the uneven distribution of epitopes may be in part due to a limited cross-recognition of specific responses because of differences between peptides used to probe the immune response and autologous strains, regions with a paucity of defined epitopes also had higher frequencies of amino acids that tend to not be found in C-terminal positions of epitopes, and had lower cleavage prediction scores for epitope processing. This suggests that in the regions of the virus where variation is best tolerated, traces of immune escape have left an imprint on the viral population. Epitopes also were concentrated in alpha-helix and turn regions in the proteins.
- In the more conserved p24, and Pol proteins RT and Protease, epitopes are more evenly distributed.

**HXB2 Location** Nef

**Author Location** Nef (HXB)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** epitope processing, vaccine-specific epitope characteristics

**References** Lu *et al.* 2000a

- Bacillus anthrax lethal toxin (LFn)-HIV fusion proteins are candidate HIV vaccines that are safe in mice, and LFn-V3 region fusion proteins induce CD8 T cells in BALBc mice. LFn causes exogenous protein to be taken up and processed in a class I pathway. Expressed proteins from Gag p24 and nef fragments cloned into the LFn expression plasmid stimulate gag-specific CD4 proliferation and CTL responses in HIV-infected donor PBMCs *in vitro*.

**HXB2 Location** Nef

**Author Location** (BRU)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression

**References** Edwards *et al.* 2002

- 96% (26/27) chronically infected HIV-1 infected patients elicited gamma-IFN CD8+ T-cell responses against Gag.
- Nef and/or Pol CTL responses were detected in 86% of the subjects.
- The magnitude and breadth of Gag and p24 T-cell responses correlated with absolute CD4 counts, and inversely correlated with viral load.
- Pol and Int CTL responses correlated positively with absolute CD4+ T-cell count.
- Nef and Env responses did not correlate with either CD4 counts or viral load.

**HXB2 Location** Nef

**Author Location**

**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, dendritic cells**References** Larsson *et al.* 2002b

- Autologous mature dendritic cells with rec vaccinia expressing Gag, Pol, Nef and Env could amplify CD8+ T-cell Elispot responses 4-38 fold in five HIV+ patients on successful HAART treatment, relative to autologous monocytes. Some weak responses could only be detected using mature dendritic cells as APCs, and this approach could be useful for detection of low frequency memory cells.

**HXB2 Location** Nef**Author Location** (SF2)**Epitope****Subtype** B**Immunogen** HIV-1 and HCV co-infection**Species (MHC)** human**Keywords** rate of progression**References** Lauer *et al.* 2002

- HIV-1 and HCV immune responses were studied in 22 individuals who were co-infected with HIV-1 and hepatitis C virus (HCV). IFN $\gamma$  production was measured in an Elispot assay of CD8+ T-cells using targets expressing either Gag, RT, Env and Nef in a vaccinia construct, or one of seven HCV proteins.
- All 22 patients targeted at least one protein. 20/22 patients recognized RT, 17/22 patients recognized Gag, 13/22 subjects recognized Env and 11/22 patients recognized Nef. Robust CTL activity was independent of disease progression or viral load.
- Despite high HCV viral loads, very few HCV CD8+ T-cell Elispot responses were detected. In a control HCV infected person who did not have HIV-1, strong anti-HCV responses were mounted.
- HIV-specific CD4 proliferative responses were detected in 9/17 coinfecting patients, but no HCV responses were detected.

**HXB2 Location** Nef**Author Location****Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, responses in children**References** Scott *et al.* 2001

- CTL responses before and after initiation of ART were studied in 13 HIV-1 vertically infected infants <6 months of age, and 4 that were >6 months of age.
- Before ART 2/13 infants <6 months of age showed IFN $\gamma$  Elispot CD8+ T-cell responses, one to Nef and one to Env and Nef, and these responses became undetectable after successful therapy— 3 infants were coinfecting with CMV and all 3 had CMV-specific CD8+ T-cell responses.
- One older infant, at 23 months, had CTL responses against all for proteins tested, Gag, Pol, Nef and Env, and had the lowest plasma viremia of the study group. 3/4 infants older than 6 months of age responded to either Nef or Pol.

- Administration of ART over 48 weeks broadened the HIV-1-specific CTL response in 2/4 of the older children that were incomplete responders.

**HXB2 Location** Nef**Author Location** (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, supervised treatment interruptions (STI)**References** Ortiz *et al.* 2001

- Immune responses in eight chronically HIV-1 infected patients undergoing HAART therapy structured treatment interruptions (STI) were studied. STI boosted HIV-1 specific CTL responses and elevated CTL responses were maintained up to 22 weeks after the last treatment interruption, but viral load rebounded to pretreatment levels and CD4 T-cell count decline was observed. CD8 responses in PBMC were measured by cytokine flow cytometry with gp160, Gag p55, RT-Pol and Nef expressed in vaccinia.

**HXB2 Location** Nef**Author Location****Epitope****Immunogen** vaccine*Vector/Type:* adenovirus *HIV component:* Gag-Pol, Nef, Vpr**Species (MHC)** mouse**References** Muthumani *et al.* 2002

- Vpr can cause cells to go into G2 arrest, and it suppresses immune cell activation and inflammatory cytokine production, so co-immunization of BALB/c mice with recombinant adenovirus expressing Vpr and HIV-1 antigens Nef or Gag/Pol was tested to see if Vpr reduced the immune response to the other HIV antigens.
- Vpr compromised CD8+ T-cell lytic responses and T-helper proliferative responses in mice co-immunized with Vpr and Nef or Gag/Pol.
- In vitro, Vpr reduced T-cell cytokine production of IL-12 and TNF $\alpha$ , indicative of Vpr-mediated immune suppression.

**HXB2 Location** Nef**Author Location** Nef**Epitope****Subtype** multiple**Immunogen****Species (MHC)** human**Assay type** Flow cytometric T-cell cytokine assay**Keywords** subtype comparisons**References** Currier *et al.* 2003

- CD8-cellular immune responses from 21 HIV-1 infected patients from Kenya infected with subtype A, C, D, and unique recombinants were studied for cross-recognition of Gag, Env, and Nef vaccinia-expressed proteins representing subtypes A-H, including CRF01.



- Both subtype-specific and cross-reactive CTL were observed, with a skewing of responses towards the infecting subtype in the nine subjects with full length sequence available. The magnitude of the responses to Gag were the highest, less to Nef, and still less to Env.
- For Gag, 8/21 subjects responded to at least 7/8 different subtype proteins, 7 had a mixed response, recognizing some subtypes but not others, and 6 responded to only one or none of the different subtype proteins. For Env, 4/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 7 responded to one or none. For Nef, 5/19 subjects responded to at least 7/8 subtypes, 8 had a mixed response, and 6 responded to one or none.

**HXB2 Location** Nef  
**Author Location** Nef (B.AU.AF064676)  
**Epitope**  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human  
**References**

- HXB2 Location** Nef  
**Author Location** Nef  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** assay standardization/improvement  
**References** Draenert *et al.* 2003
- Six different HIV-1 Nef peptide sets ranging in length from 15-20 amino acids with overlap from 10-11 amino acids derived from either the B clade consensus sequences or the B clade sequence B.AU.AF064676 were used to study the impact of using different peptide design strategies to detect CD4 and CD8 T-cell responses. 20 individuals were tested using the six sets of peptides. 17/20 had CD8 T-cell responses to all peptides sets, and 15 of these 17 had CD4 T-cell responses.
  - Although there was a trend in detecting more CD8 T cell responses using the shorter 15-mer peptides, longer 20-mers were best for detecting more CD4 T-cell responses, but neither result was statistically significant. Similar results were seen in the 15 to 20 amino acid range for both IFN gamma Elispot and ICS assays.
  - Use of the consensus versus the natural strain identified slightly increased numbers of reactive peptides. Seven reactive peptides were observed with the B consensus peptides but not the B.AU.AF064676 peptides, but on the other hand four reactivities were observed using the B.AU.AF064676 peptides but not the consensus.
  - Using an overlap of 10 or 11 amino acids did not make a difference.

**HXB2 Location** Nef  
**Author Location** (C consensus)  
**Epitope**  
**Subtype** C  
**Immunogen** HIV-1 infection

- Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Novitsky *et al.* 2003
- In this study, PBMC from 105 asymptomatic HIV-1 C clade infected patients from Botswana were screened for HIV-1 subtype C specific T-cell responses directed against Gag, Pol, Vif, Vpr, Tat, Rev, Vpu, Env and Nef. Nef-specific T-cell responses positively correlated with plasma viral load. In contrast, HIV-1 Gag and especially Gag p24 showed an inverse correlation with viral load.

**HXB2 Location** Nef  
**Author Location** (C consensus)  
**Epitope**  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression  
**References** Novitsky *et al.* 2003

- In this study, PBMC from 105 asymptomatic HIV-1 C clade infected patients from Botswana were screened for HIV-1 subtype C specific T-cell responses directed against Gag, Pol, Vif, Vpr, Tat, Rev, Vpu, Env and Nef. Nef-specific T-cell responses positively correlated with plasma viral load. In contrast, HIV-1 Gag and especially Gag p24 showed an inverse correlation with viral load.

**HXB2 Location** Nef  
**Author Location** Nef  
**Epitope**  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, immunodominance, acute/early infection, early-expressed proteins  
**References** Masemola *et al.* 2004a

- Anti-HIV T-cell responses in subtype C HIV-1 infected individuals in the beginning of the infection target multiple protein regions, but the responses are dominated by Nef, making up almost one-third of the total responses. 97.5% of the Nef epitopes targeted were within a short stretch of 119 amino acids.
- Neither breadth nor magnitude of CD8+ T-cell responses were correlated with control of virus, however hierarchical preferential targeting of Gag was significantly associated with lower viral loads.

**HXB2 Location** Nef  
**Author Location** Nef (B consensus)  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HAART, ART, immunodominance, acute/early infection, vaccine antigen design

**References** Lichterfeld *et al.* 2004b

- HIV-1 specific CD8 T-cell responses in individuals with acute and early HIV-1 infection are preferentially directed against epitopes in the central region of Nef, with 94% of the magnitude of the response in acute infection directed at Nef, and 46% during early infection. In chronic infection, CD8 T-cell immune responses are broadly diversified towards Gag, Env and Pol, and Nef accounts for only 17% of the response.
- The region of Nef that is targeted is the central most conserved region, but relative to other HIV proteins it is still quite variable. However, responses are cross-reactive enough to detect strong acute responses using consensus based peptides, and is an early expressed gene so may have advantages in the context of a vaccine.
- Nef immunodominance was retained in patients that were treated during acute infection, but no treatment and so continuous antigen exposure resulted in rapid diversification of the immune response.

**HXB2 Location** Nef

**Author Location**

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promoter  
*Strain:* B clade HXB2, B clade NL43, A clade 92RW020, C clade 97ZA012  
*HIV component:* Env, Gag, Nef, Pol

**Species (MHC)** human

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** therapeutic vaccine

**References** Catanzaro *et al.* 2006

- 14 volunteers uninfected with HIV completed a set of injections with a 6-plasmid DNA vaccine encoding EnvA, EnvB, EnvC, and subtype B Gag, Pol, and Nef. CD4 and CD8 T cell responses to Env and Gag were most frequently detected.
- For Nef, 3/14 subjects showed a positive CD8+ T cell response by ICS.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection, in vitro stimulation or selection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** immunotherapy

**References** Kavanagh *et al.* 2006

- Transfection of antigen-presenting cells with a clade B consensus nef construct bearing lysosomal targeting signals produced rapid and prolonged antigen presentation to CD4+ and

CD8+ T cells. Lysosome-targeted antigen drove a significantly greater expansion of Nef-specific CD4+ T cells, compared with cytoplasm-targeted antigen.

## II-B-24 HIV-1 CTL/CD8+ epitopes

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Subtype** CRF01\_AE

**Immunogen** vaccine

**Species (MHC)** human (A11)

**Keywords** review, vaccine-specific epitope characteristics, escape

**References** Ariyoshi *et al.* 2002

- This review summarizes a meeting held to discuss options for determining CTL responses to vaccines. Problems are noted: costs for some assays are prohibitive for a Phase III study, Elispot shows interlaboratory variation but could be extended to many samples. HLA-A11 is very common in Thailand – over 30% carry the HLA-A11 allele. Predominant strains may be evolving to evade recognition of A11 restricted epitopes. Few full length CRF01 sequences are available. Epitopes may differ in vaccinees and infected individuals.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human (A11, B40, B8, Cw8)

**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** HAART, ART, acute/early infection, early treatment

**References** Alter *et al.* 2003

- Longitudinal study (24 mo) monitoring T-cell immune responses in 4 patient groups: Group 1 (n=6) consists of subjects who underwent HAART preseroconversion, group 2 (n=11) were HAART treated during early postseroconversion, group 3 (n=5) contained patients who started HAART during late postseroconversion, and group 4 (n= 6) commenced with HAART during chronic HIV-1 infection.
- The experimental strategy was to test for reactivity levels with sets of peptides that each contain epitopes with known HLA-restricting elements, making the peptide selection based on the optimal epitope list in this database. The HLA alleles found in the patients were balanced so that the frequency in the groups were comparable. Peptides spanning parts of Gag, Env, Nef, and RT were used for Elispot, and Gag peptides were used for ICS.
- All group 1 patients, and 5/11 group 2 patients, maintained the breadth and the magnitude of the immune response throughout the study; those in group 2 that maintained response started therapy earlier. The hierarchy of intensity of responses to different peptides was preserved. Individuals in groups 3 and 4 all showed a decline, and after treatment lost responses. Groups 1 and 2 showed HAART-induced suppression of viremia but maintained responses. Groups 3 and 4 both

showed viral suppression in association with a decreased immune response in breadth and magnitude after HAART. The authors suggest that preservation of HIV CD4+ responses can be maintained even if HAART is first given beyond the acute phase of infection, and a delay may allow a full CD8 response to develop while still allowing CD4 function to be preserved.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine**Species (MHC)** human (B27, B8)**Keywords** binding affinity, review, subtype comparisons, epitope processing, escape**References** McMichael & Hanke 2002

- CTL response-eliciting vaccines are reviewed. The natural epitope interactions with the HLA class I presenting molecules and T-cell receptors are described, and the impact of breadth of CTL responses and diversity considered in a vaccine context.
- Interesting specific examples are given concerning anchor chain residues. For B27, the B pocket fits Arg (R) but not Lys (K), so even this conservative change is not tolerated. In B8 either R or K can fit in the B pocket, but the substitution will cause conformational shifts in other parts of the epitope.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine*Vector/Type:* Listeria monocytogenes *HIV component:* Gag**Species (MHC)** mouse (H-2<sup>d</sup>)**Keywords** review**References** Lieberman 2002

- Attenuated Listeria monocytogenes vectors elicit strong persistent CTL responses in vaccinations of BALB/c mice and can protect mice from a vaccinia-gag challenge.

**HXB2 Location** HIV-1**Author Location** gp120 (V3) and p24 (IIIB, MN, BH10)**Epitope****Subtype** A, B**Immunogen** vaccine*Vector/Type:* virus-like particle (VLP)  
*Strain:* A clade UG5.94UG018, B clade IIIB  
*HIV component:* Gag, gp120**Species (MHC)** mouse (H-2<sup>d</sup>)**Assay type** Chromium-release assay**Keywords** subtype comparisons**References** Buonaguro *et al.* 2002

- Different HIV strains were used for different regions: gp120 A clade UG5.94UG018, and B clade IIIB
- BALB/c mice were given intraperitoneal immunization with virus-like particle (VLPs) expressing recombinant subtype A gp120 and Pr55gag in the absence of adjuvants.
- High dose-independent humoral responses against both gp120 and p24 peptides were detected. Antibodies able to elicit 50% neutralization against A clade IIIB and the autologous clade a virus were obtained.

- Recombinant rgp120 (clade B, MN) induced T-cell proliferative responses *in vitro* from vaccinated animals.
- CTL activity was observed against splenocytes expressing Env (clade A) and Gag (clade B, BH10) from a vaccinia construct.

**HXB2 Location** HIV-1**Author Location****Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* DNA, polyepitope *Strain:* A clade, B clade *HIV component:* Env, Gag, Pol *Adjuvant:* IL-12, IL-2, liposome**Species (MHC)** mouse (H-2<sup>d</sup>)**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Delayed-type hypersensitivity (DTH), Chromium-release assay**Keywords** vaccine-induced epitopes**References** Shinoda *et al.* 2004

- Mice immunized with a polyepitope DNA vaccine encoding 20 antigenic epitopes of several HIV-1 clades (hDNA vaccine) showed strong Ab responses, activation of IFN-gamma secretion cells targeting gp120 and synthetic antigenic peptides, and several peptide specific CTL responses. When challenged with recombinant HIV-vaccinia viruses, mice immunized with the hDNA vaccine showed lower viral titers in the ovary.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Schito *et al.* 2001

- Longitudinal analysis (72 weeks) of 15 patients with acute or recent HIV-1 infection implies that HAART treatment alone can not completely conserve CD8+ cell homeostasis and preserve the original T-cell receptor repertoire.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Mackewicz *et al.* 2000

- Non-cytotoxic anti-HIV responses of CD8+ T cells cultured with CD4 infected HIV cells are mediated by blocking expression of viral RNA, and do not influence viral replication steps through integration of provirus.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine**Species (MHC)****Keywords** dynamics**References** Altes *et al.* 2002

- This study employs a mathematical model to study the consequences of increasing the T-helper response through a vaccine, which would have counter-balancing effects in a new infection: a more intense response provides more help but also more target cells. The model indicates that if the infecting virus had a low replication rate, then CTLp and CD4 helper cells could control an infection. Only a vaccine that could increase CTL responsiveness could reduce viral set point with observed replication rates.
- A CD4+ T-cell response without maintained CTL response was deleterious in this model.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** assay standardization/improvement**References** Carrier *et al.* 2002b

- Elispot standardization was sought using a reference peptide pool of 23, 8-11 mer epitopes from Influenza, cytomegalovirus (CMV), and Epstein Bar Virus (EBV) presented by 11 common HLA class I molecules.
- 15/17 (88%) HIV- and 14/20 (70%) HIV+ individuals reacted with this test set and *in vitro* simulation of the PBMC from these individuals were capable of killing cells expressing the target antigen.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human, macaque**Keywords** dynamics, HAART, ART**References** Wodarz 2002

- Mathematical modeling is used to support the idea that T-helper cell dysfunction results in a compromised ability to maintain an anti-HIV CTL memory response. Models suggest strategies to restore CTL memory through therapy and improve long-term immunological control of the virus.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection, vaccine**Species (MHC)** human**Keywords** review**References** Zinkernagel 2002

- HIV immunity and vaccine strategies are compared with to other pathogens. We do not have a successful vaccine against TB leprosy, HIV, HCV and most parasites, and the author suggests this is associated with the need for a strong T-cell response to these diseases. Vaccine strategies that achieve a physiological low does infection that is well controlled but persists may be required to alter the immunopathological consequences of infection with HIV.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine**Species (MHC)** human**Keywords** review, subtype comparisons, epitope processing**References** Gaschen *et al.* 2002

- The concept of using an artificial consensus sequence for vaccine design is discussed, comparing the concepts of a model ancestor sequence or a consensus sequence, with illustrations of the potential advantages of the strategy based on C-clade comparisons.
- See also a comment Nickle *et al.* [2003], and reply Gao *et al.* [2003]

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human, macaque**Keywords** review, class I down-regulation by Nef, escape**References** Johnson & Desrosiers 2002

- Reviews evidence for CTL escape in HIV epitopes in natural human infections, and in SIV infections of macaque where viral clones with a known time of infection and multiple animals with the same HLA molecules can be tracked.
- Vigorous CTL responses are made despite class I down-regulation by the Nef protein, but it may delay cytolysis of infected cells. Too great a loss of MHC proteins may enhance NK cell killing so the fitness advantage of this function of Nef may be in balance.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection, vaccine**Species (MHC)** human**Keywords** review, epitope processing, supertype, computational epitope prediction, HIV exposed persistently seronegative (HEPS), supervised treatment interruptions (STI), immunodominance**References** Newman *et al.* 2002

- This extensive review covers many aspects of T-cell immunity and natural HIV infections, and considers how this knowledge might be applied to a polyepitope vaccine approach. Strategies concerning ways to avoid the creation of junctional epitopes and use of linkers to enhance processing of such constructs are discussed.
- The C-terminal flanking residue (C1) was found to be associated with immunodominance of epitopes, such that R or K (positive charge) > N or Q (amide) > C, G, A, T, S (small) > F, W, Y (aromatic) > I, L, M, V (aliphatic) > D (negative). As this position is outside and proximal to the epitope, processing and cleavage is the likely reason for this observation.
- Changing the C1 residue from F to K for an HLA-A2 presented epitope from HBV resulted in a change from the epitope being non-immunogenic to strongly immunogenic.

**HXB2 Location** HIV-1**Author Location**

- Epitope**  
**Immunogen** HIV-1 infection, vaccine  
**Species (MHC)** human  
**Keywords** review, HIV exposed persistently seronegative (HEPS)  
**References** Johnston & Flores 2001
- Reviews the current state of HIV vaccine approaches, and discusses the role of CTL induced immunity in protection or partial protection in animal studies, likening it to the CTL found in HEPS studies.
- HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** binding affinity, review, escape  
**References** Klenerman *et al.* 2002
- The importance of breadth, or spread, of CTL responses is discussed, as narrowly focused responses can be more readily escaped.
  - Some HLA types and specific epitope recognition may be associated with a better disease outcome. Reasons for this are considered, including NK cell activity, epitope affinity, epitope conservation, and class I specific induction of more effective T-cell receptors.
- HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** review, HIV exposed persistently seronegative (HEPS), responses in children, mother-to-infant transmission  
**References** Kuhn *et al.* 2002
- Intrauterine exposure of infants to HIV from their mothers results in HIV-1 specific T-helper cell proliferative responses in 1/3 of exposed uninfected babies, and HIV-1 specific CTL in some. Such responses are evident, but it is unknown whether they are associated with lack of infection, but there is some evidence that HIV-1 T-cell responses may reduce transmission in breastfeeding mothers. Summary tables are provided of CD4 and CD8 responses detected in earlier studies.
- HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** HIV exposed persistently seronegative (HEPS), mother-to-infant transmission  
**References** Kuhn *et al.* 2002; Levy *et al.* 1998
- A non-HLA-specific, non-chemokine-mediated CD8+ T-cell non-cytotoxic anti-HIV response, measured by suppression of acute viral infection of CD4 cells, was detectable in approximately 16/31 (52%) of uninfected children born of infected mothers, was more commonly detected in those <1 year old, and could reflect a protective response.

- Reviewed in Kuhn *et al.* [2002].

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** vaccine

**Species (MHC)** human

**Keywords** dynamics

**References** Altes *et al.* 2001

- Mathematical modeling suggests if the effector CTL vaccine response exceeds the level of response seen in chronic infection, that a memory CTL population is established that can respond very quickly to protect from infection.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** vaccine

**Species (MHC)** human

**Keywords** review

**References** Copeland 2002

- This review summarizes cytokines and chemokines produced by CD8+ T-cells that can interfere with HIV's infection and replication.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** vaccine

**Species (MHC)**

**Keywords** review

**References** Edgeworth *et al.* 2002

- This review summarizes HIV vaccine strategies, adjuvants, current clinical trials and animal models.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** vaccine

**Species (MHC)**

**Keywords** review

**References** Graham 2002

- This review summarizes HIV vaccine approaches and clinical trials.

**HXB2 Location** HIV-1

**Author Location** Env (HXB2)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade HXB2

*HIV component:* gp140ΔCFI, gp160 deletions

**Species (MHC)** guinea pig, mouse

**References** Chakrabarti *et al.* 2002

- Intramuscular injection of plasmid DNA was used to vaccinate BALB/c or Huntley guinea pigs with a series of codon-optimized modified HIV-1 HXB2 envelopes – modifications included elimination of glycosylation sites, deletions, and exchange of the V3 loop to change from a X4 or R5 phenotype.

- The mutant envelope gp140deltaCFI gave the most promising result, enhancing antibody responses while retaining the ability to stimulate a strong CTL response.
- gp140deltaCFI has deletions in the cleavage site, fusogenic domain and spacing of the heptad repeats, and was designed to mimic a fusion intermediate.

**HXB2 Location** HIV-1**Author Location** Env (gp160) (384–467)**Epitope****Immunogen** vaccine*Vector/Type:* hepatitis B surface antigen lipoprotein particles (HsBAg) *Strain:* B clade LAI *HIV component:* V3**Species (MHC)** macaque, rabbit**References** Michel *et al.* 1993

- Immunization with recombinant HIV1 V3/HBsAg hybrid particles into rabbits or macaques elicited and maintained for several months anti-V3 or HIV-1 Env proliferative, CTL and Ab responses.

**HXB2 Location** HIV-1**Author Location** Gag (HXB2)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Garba *et al.* 2002

- CD8+ Tcells from 25% of HIV positive individuals produce TGF-beta1 in response to stimulation with HIV proteins, and this can significantly reduce CD8+ T-cell IFN-gamma induction to HIV and vaccinia proteins.
- Different peptides can preferentially induce TGF-beta1 or IFN-gamma from CD8+ T-lymphocytes from the same individual, and TGF-beta1 non-specifically suppresses HIV-specific immune responses.

**HXB2 Location** HIV-1**Author Location** Pol (HXB2)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Garba *et al.* 2002

- CD8+ Tcells from 25% of HIV positive individuals produce TGF-beta1 in response to stimulation with HIV proteins, and this can significantly reduce CD8+ T-cell IFN-gamma induction to HIV and vaccinia proteins.
- Different peptides can preferentially induce TGF-beta1 or IFN-gamma from CD8+ T-lymphocytes from the same individual, and TGF-beta1 non-specifically suppresses HIV-specific immune responses.

**HXB2 Location** HIV-1**Author Location** Env (MN)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Garba *et al.* 2002

- CD8+ Tcells from 25% of HIV positive individuals produce TGF-beta1 in response to stimulation with HIV proteins, and this can significantly reduce CD8+ T-cell IFN-gamma induction to HIV and vaccinia proteins.
- Different peptides can preferentially induce TGF-beta1 or IFN-gamma from CD8+ T-lymphocytes from the same individual, and TGF-beta1 non-specifically suppresses HIV-specific immune responses.

**HXB2 Location** HIV-1**Author Location****Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining**Keywords** assay standardization/improvement, acute/early infection**References** Altfeld *et al.* 2003

- The frequency of HIV-1 specific T-cell responses was characterized in an Elispot IFN-gamma assay, using 507 overlapping peptides based on the B clade consensus sequence spanning all HIV-1 clade B proteins against PBMC from 57 HIV-1 infected patients at various disease and treatment stages. 63% of the peptides were recognized (range of 1-42 per subject, median=14). More variable peptides were targeted less frequently.
- Autologous virus sequences from six patients in acute infection spanning of HIV-1 p24, Tat and Vpr were used to scan for missed responses due to viral variation when using the consensus for peptides. 12/42 (29%) responses to these peptides were detected only with autologous peptides, and often these autologous responses were immunodominant. Responses were also generally higher using autologous peptides.
- A longitudinal analysis (5 yrs) of the T-cell responses in 5 patients showed that the autologous sequence detected stronger T-cell recognition than the HIV-1 clade B consensus sequence.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** chimpanzee**Keywords** review**References** Balla-Jhagjhoorsingh *et al.* 2003

- This paper reviews HIV-1-specific cell-mediated immune responses in chimpanzees and discusses mechanisms that might control HIV-1 pathogenesis in chimpanzees. During the first decade of the HIV epidemic, more than 200 chimpanzees were experimentally infected with HIV. Among these only one case of declining CD4+ cells has been reported, all others have remained asymptomatic with no loss of immune function, some after 20 years of infection. In contrast to infected humans which have a skewed Th2 response, chimpanzees maintain balanced Th responses and are likely to support a fully mature CD8+ T-cell response.

- Specific HIV epitopes recognized by chimpanzees have been mapped and CTL detected, but overall the responses are at much lower levels than in humans, as viral loads are so low. Gag epitope responses are estimated to be 0.0095 to 0.0025% of the CD8+ T cell population in chimpanzee, and 1-2% in humans.
- The authors argue that the chimpanzee immune response may be effective at controlling virus because it focuses on conserved epitopes, and further speculate that long contact with lentiviruses may have put strong selection pressures on the chimpanzee MHC class I, narrowing the population's ability to respond to only the most conserved, and so useful, epitopes.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Fagard *et al.* 2003

- This study monitored the effects of repeated treatment interruptions (STI), in 2-week intervals, in 133 HIV-1 infected, HAART-treated patients. STIs were rarely able to control viremia without continued HAART, and increases in CD8+ T-cell response frequencies did not correlate with the level of control of viral replication. CD8+ T cell responses were measured by gamma IFN Elispot using between 2-32 different optimal HIV epitopes, selected to be appropriate for the patient's HLA type.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen**

**Species (MHC)** human

**References**

**HXB2 Location** HIV-1

**Author Location** HIV-1

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** responses in children

**References** Feeny *et al.* 2003

- The magnitude and breadth of CD8+ T-cell responses in 18 pediatric (6-17 years) perinatally HIV-1 infected patients was determined using 1) overlapping peptides spanning all HIV-1 proteins and 2) peptides from all predefined appropriately class I HLA-restricted HIV-1 epitopes.
- Perinatally infected children's CD8+ T-cell responses were comparable in magnitude and breadth to adult responses. Many reactive peptides did not overlap with a previously characterized optimal epitope.

- On average 20% of all known pre-defined optimal epitopes presented by appropriate HLAs were recognized in these children. In two patients, autologous sequences spanning unrecognized potential epitopes usually corresponded to the reactive form of the epitope, so epitope variation alone did not account for unrecognized epitopes.

- Children with detectable viremia showed a broader and greater CTL responses than HAART responsive children with undetectable viremia.

**HXB2 Location** HIV-1

**Author Location** HIV-1

**Epitope**

**Immunogen**

**Species (MHC)**

**References**

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** vaccine

**Species (MHC)**

**Keywords** review

**References** Hanke 2003

- Review of HIV vaccine development discussing diversity, the merits and difficulties of stimulating different arms of the immune response, and different strategies, including DNA vaccines, viral vectors, CTL epitope based, and protein- or peptide-based vaccines.

**HXB2 Location** HIV-1

**Author Location** HIV-1 (HXB2)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Hladik *et al.* 2003

- Longitudinal study analyzed IFN- $\gamma$  CD8+ T cell responses in highly exposed, seronegative homosexual men. Overlapping peptides spanning the Gag, Env, Nef and Pol subtype B HXB2 sequence were used to stimulate PBMC from 26 individuals, whose frequency of HIV-1 specific IFN- $\gamma$  T cell responses were very low.
- CD8+ T cells from 3/15 individuals (EES15, ES29, and ES63) recognized > 3 peptide pools.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** Chromium-release assay

**Keywords** dynamics

**References** Kousignian *et al.* 2003

- The diversity of HIV protein (Gag, Pol, Env, Nef, Rev, Tat, Vif) recognition by CTLs was studied longitudinally in a cohort of 152 HIV-infected untreated individuals, and was analyzed by Markov modelling. CTL responses from 152 HIV-1 infected patients in four stages of disease progression were collected for a period of 5 years. Results show that memory CTL responses against HIV-1 proteins are acquired during early HIV-1 infection and subsequently lost. As viral load increased there was an accelerating loss of multiple protein recognition.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection, vaccine*Vector/Type:* gp120 depleted whole killed virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA)**Species (MHC)** human**References** Lederman & Douek 2003; Robbins *et al.* 2003

- Lederman and Douek is an editorial comment referring to the study presented by Robbins *et al.*, in which the authors discuss why an HIV-1 gp120-depleted inactivated HIV vaccine elicits HIV-1 specific T helper responses in 5/5 HIV+ people, but not CD8+ CTL responses. In chronically infected people it appears that stimulating Th responses in and of itself is not enough to restore strong CTL responses.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine*Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72), CpG immunostimulatory sequence (ISS), HSP70**Species (MHC)** human**Keywords** review, Th1, Th2, genital and mucosal immunity**References** Lehner 2003

- This review discusses the importance of mucosal and innate immunity for future vaccination strategies in HIV infection in humans. Different mucosal adjuvants are compared, and the advantages of a Th1 polarized response.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Onyemelukwe & Musa 2002

- Longitudinal study (1991-1997) of the clinical presentation of 80 HIV-1 or HIV-II seropositive people in Zaria, Nigeria, who contracted HIV-1 primarily via heterosexual transmission. Main complicating diseases were tuberculosis and bacterial infections including Salmonella, Streptococcus pneumoniae and Staphylococcus. HIV-1 progression was associated with a decline of not only CD4+ T cells, but CD8+ T cells as well – patients had CD4+ counts < 200 cells/ul, and CD8 counts were 190 cells/ul versus 440 cells/ul for controls.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Onyemelukwe & Musa 2002

- Longitudinal study (1991-1997) of the clinical presentation of 80 HIV-1 or HIV-II seropositive people in Zaria, Nigeria, who contracted HIV-1 primarily via heterosexual transmission. Main complicating diseases were tuberculosis and bacterial infections including Salmonella, Streptococcus pneumoniae and Staphylococcus. HIV-1 progression was associated with a decline of not only CD4+ T cells, but CD8+ T cells as well – patients had CD4+ counts < 200 cells/ul, and CD8 counts were 190 cells/ul versus 440 cells/ul for controls.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ **Keywords** HAART, ART**References** Price *et al.* 2003

- CD4+ and CD8+ T cell responses were analyzed in this longitudinal study (19 mo) of 53 patients with chronic HIV-1 infection receiving continuous ART therapy. Three subgroups were compared: one with suppressed viremia and increasing CD4+ T cell counts, one with detectable viral load and declining CD4, and one with detectable viral load with a positive CD4+ T cell slope.
- IFN- $\gamma$  ELISPOT analysis was performed with peptides spanning RT, Env, Gag (p24), Gag(p17), Nef, Tat and Rev. The IFN- $\gamma$  analysis showed the greatest CD4+ as well as CD8+ T-cell responses in the group with stable CD4+ T cell responses despite detectable virus over a median time course of 9 months.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen****Species (MHC)** human**Assay type** Chromium-release assay**Keywords** rate of progression**References** Sindhu *et al.* 2003a; Sindhu *et al.* 2003b

- In a cross-sectional study of 31 HIV+ people, a correlation was observed between CTL-mediated bystander HLA-unrestricted lysis of primary CD4+ T-cells.  $\gamma\delta$  CTL are abnormally expanded in HIV+ people, and the V $\delta$ 1 subset can deplete bystander CD4+ T-cells and expedite progression. In a set of 13 patients, an inverse correlation was observed between CD8+ T-cell activation markers and viral load, thought to be an indicator of CTL-associated immunopathogenesis in HIV progression.

**HXB2 Location** HIV-1**Author Location****Epitope**



**Immunogen** HIV-1 infection  
**Species (MHC)**  
**Keywords** review  
**References** Vella & Daniels 2003

- This article reviews the CD8+ T-cell antiviral factor (CAF). CAF contributes to MHC restricted, CD8+ T-cell mediated non-cytolytic suppression of HIV in infected individuals.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Subtype** A, B, C

**Immunogen** vaccine

*Vector/Type:* DNA, polyepitope *HIV component:* gp120, gp41, Nef, p17 Gag, p24 Gag, Pol *Adjuvant:* concavalin A-immobilized polystyrene nanospheres

**Species (MHC)** mouse

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$

**Keywords** vaccine-induced epitopes

**References** Bazhan *et al.* 2004

- A synthetic T cell polyepitope immunogen containing 80 overlapping Env, Gag, Pol and Nef epitopes was used to immunize mice. It induced both humoral and cellular responses which increased upon reimmunization.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen**

**Species (MHC)**

**Keywords** review, class I down-regulation by Nef, early-expressed proteins, immune evasion

**References** Collins 2004

- There are a number of factors that combined make HIV-infected cells resistant to CTLs. HLA-associations with disease progression are reviewed. Nef down-regulation of HLA class I A and B molecules is one important mechanism of HIV immune evasion. Rev allows late viral proteins to be expressed, enabling CTL specific for epitopes in these proteins to recognize infected cells. It is suggested that blocking the activity of Nef and Rev would reduce production of viral variants and enhance the ability of CTLs to combat HIV.

**HXB2 Location** HIV-1

**Author Location** (SIV)

**Epitope**

**Immunogen** SIV infection

**Species (MHC)** macaque

**Keywords** escape, viral fitness and reversion

**References** Friedrich *et al.* 2004

- SIV CTL escape variants revert to wild-type epitopes after transmission to new hosts with disparate MHC class I alleles. Thus mutations in CTL epitopes may have moderate to severe negative effects on viral replicative fitness although some escape variants are shown to accumulate substitutions in flanking regions of the epitope that help compensate for fitness loss.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen**

**Species (MHC)** human

**Keywords** dynamics, HAART, ART

**References** Ganasov 2003

- The rate of virus decline after initiation of HAART is shown by a mathematical model, to depend on whether the virus is controlled by the CTL response via lytic or non-lytic mechanisms.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** review, class I down-regulation by Nef, escape, dendritic cells, TCR usage, memory cells, immune dysfunction

**References** Gulzar & Copeland 2004

- HIV has developed numerous strategies to evade CD8+ T-cell response that are reviewed in this paper, including escape mutations in CD8+ T-cell recognition, down-regulation of MHC-I surface expression, alternating cytokine production, disruption of proper CD8+ T-cell signaling resulting in anergy, and disruption of the function of CD4+ T-cells and APCs required for CD8+ T-cell maturation.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** characterizing CD8+ T cells

**References** Kitchen *et al.* 2004

- This paper characterizes a population of cells that are CD3+, CD8+, and CD4+. These cells are mature and highly activated. The CD4 molecule expressed by these CD8+ T-cells plays an important role in expression of IFN-gamma and Fas ligand and cytotoxic responses. HIV infection of CD8+CD4+ T-cells results in Nef independent down-regulation of CD4 and dysregulation of IFN-gamma and Fas ligand, and provides an additional reservoir for the virus.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen**

**Species (MHC)** human

**Keywords** review, characterizing CD8+ T cells

**References** Petrovas *et al.* 2004

- This review discusses the attributes of HIV-specific CTLs that contribute to their inability to control HIV infection, with an emphasis on the susceptibility of HIV-specific CTL to CD95/Fas induced apoptosis upon binding target cells. Furthermore, Nef may inhibit apoptosis by blocking CD95/Fas signaling on infected cells.

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United Kingdom  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , T-cell Elispot, Flow cytometric T-cell cytokine assay  
**Keywords** HAART, ART, immune dysfunction  
**References** Pires *et al.* 2004

- Daily administration of rec human growth hormone (rhGH) induced an increase in the numbers of naive CD4 T-cells and effector CD8 T-cells. Also, a rise in HIV-1 antigen-specific CD4 and CD8 T-cell responses was observed. The function of specific effector CD8 T-cells was preserved despite an eventual decrease of specific CD4 T-cell responses.

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection, vaccine  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** review, supervised treatment interruptions (STI), vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization  
**References** Robinson 2003

- This paper is a commentary on Altfeld *et al.* Nature 420:434 2002. The patient AC-06 was superinfected with a second strain of HIV-1 after STI despite 12 of 25 recognized CD8+ T-cell epitopes maintaining strong cross-reactive immunity measured by gamma IFN EliSpot against the second strain. While vaccine trials in macaques have given optimistic results, this patient's superinfection in spite of a strong cross-reactive CD8+ T-cell immune response suggests that vaccine strategies may have to be re-examined.

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Spain  
**Assay type** Flow cytometric T-cell cytokine assay  
**Keywords** rate of progression  
**References** Rodés *et al.* 2004

- A complex set viral or host factors has been found to be associated with the absence of disease progression among long-term non-progressors (LTNP). 19 LTNP were followed for six years; 12 were non-progressors over this period, 7 showed a slow progressive CD4 depletion. Their virus replicative capacity was shown to be reduced and T-cell activation was low. Pooled peptide CD8+ T-cell gamma IFN responses did not differ between non-progressors, slow progressors, or a group of HIV progressors.

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* canarypox prime with recombinant protein boost *Strain:* B clade SF2  
*HIV component:* Env, Gag, Protease  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** assay standardization/improvement  
**References** Russell *et al.* 2003

- IFN- $\gamma$  Elispot assay is shown to be a good initial screening method for measurement of CD8+ T-cell responses in both vaccination and natural HIV-1 infection. Responses were detected using peptides at low concentrations (1-2  $\mu$ g/mL) and an increase in detection of HIV-1 specific CD8+T-cells by using 15-mers rather than 20-mer peptides for cell activation was observed. More responses were detected using smaller pools (10 or 2 peptides) than larger pools (25 or 50 peptides), so smaller pools may be needed to detect low frequency responses. Responses to natural infection were more than a log higher than to the vaccine.

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection, SIV infection  
**Species (MHC)** human, macaque  
**Keywords** review, escape, viral fitness and reversion  
**References** Smith 2004

- This paper reviews several studies which track HIV and SIV CTL escape mutations after transmission into a new host, and reversion rates and fitness costs of CTL escape. Some escape mutants have a cost to viral fitness. The author suggests that CTL based HIV-1 vaccine should therefore not only increase cellular responses against viral epitopes but also favor epitopes where escape mutations result in significant decrease in viral fitness.

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade *HIV component:* gp140, gp160 *Adjuvant:* reovirus alpha 1 protein

**Species (MHC)** mouse  
**Donor MHC** H-2d  
**Assay type** Cytokine production, Chromium-release assay  
**Keywords** adjuvant comparison  
**References** Wang *et al.* 2003

- M cells are found in the follicle-associated epithelium in mucosal inductive tissues, and reovirus are able to attach to these cells via the alpha 1 protein. Respiratory mucosal sites were targeted with a reovirus protein alpha 1 protein delivered with a DNA vaccine administered i.n. in BALB/c mice. The naked

gp160 DNA vaccine did not elicit CD8+ T cell responses, but when delivered with alpha 1 protein, CTL responses were observed in the lungs, spleens and lymph nodes. gp160 was shown to be most immunogenic compared to a cytoplasmic gp140 and secreted gp140. The vaccinated animals had reduced vaccinia virus when challenged with a vaccinia-env recombinant.

**HXB2 Location** HIV-1

**Author Location** Gag

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor, fowlpoxvirus *Strain:* SIV *HIV component:* Env, Gag, Pol, Rev, Tat, Vpu *Adjuvant:* IFN $\gamma$ , CpG immunostimulatory sequence (ISS)

**Species (MHC)** macaque

**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining

**Keywords** adjuvant comparison, vaccine antigen design

**References** Dale *et al.* 2004

- Macaques immunized with DNA and fowlpox vaccines showed high levels of CD4 and CD8 T-cell immune responses to Gag. Single DNA priming vaccination or coexpressed IFN-gamma with the fowlpox virus boost were shown to be less immunogenic and less protective than sequential DNA and fowlpox virus vaccination. Partial protective immunity was observed following a high dose, virulent SHIV challenge, for the DNA fowlpox prime boost, as well as the DNA vaccination alone, even though standard assays failed to detect a strong immune response with DNA alone.

**HXB2 Location** HIV-1

**Author Location** (IIIB, Thai B', Chinese CB)

**Epitope**

**Subtype** B, C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** China

**Assay type** Intracellular cytokine staining, Chromium-release assay

**Keywords** subtype comparisons, characterizing CD8+ T cells

**References** François-Bongarcon *et al.* 2004

- The ability of circulating T-cells from 7 North American and 4 Chinese HIV+ donors to produce IFN-gamma and/or lyse autologous primary cells infected with HIVIIIB, B' (Thai B) or C/B recombinant form was tested. The results showed cross-clade CD8 T-cell responses to the Chinese viruses among North American donors and to HIVIIIB in Chinese donors, suggesting that many of the T-cell responses to clade B virus epitopes are conserved across clades. Lysis of cells by N. American donor CD8+ T cells infected with IIIB or a Thai B' strain were comparable, while lysis infected with the Chinese BC recombinant was somewhat reduced, although the reduction was not statistically significant.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada

**Assay type** Cytokine production, Chromium-release assay, Flow cytometric T-cell cytokine assay

**Keywords** TCR usage, memory cells, characterizing CD8+ T cells, immune dysfunction

**References** Gamberg *et al.* 2004b

- A relationship was found between the proportion of HIV-specific CTLs expressing CD28 and CD4+ T-cell counts, viral load and disease progression. This association cannot be linked to disease related degeneration of CD8+CD28- T-cells in terms of their TCRbetaV family repertoire diversity or ability to produce cytokines. This suggests that effective immune responses contain CD8+CD28+ T-cell populations that shift to CD8+CD28- in ineffective responses.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen**

**Species (MHC)**

**Keywords** review, epitope processing, vaccine-specific epitope characteristics, rate of progression, immunodominance, escape, acute/early infection, early-expressed proteins, TCR usage, viral fitness and reversion

**References** Goulder & Watkins 2004

- CTLs have a central role in the control of HIV infection. Emergence of escape variants to CTLs is one of the major obstacles to vaccine development. Factors that should be considered for the development of an HIV vaccine are CTLs that are specific for epitopes recognized during the acute phase of infection, CTLs that are able to efficiently control viral replication, and epitopes from regions of the viral genome that are highly conserved or where variation results in loss of viral fitness.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)** human

**Country** Kenya

**Assay type** Chromium-release assay

**Keywords** HIV exposed persistently seronegative (HEPS), characterizing CD8+ T cells

**References** Kaul *et al.* 2004

- HIV-1 specific CTL responses found in HIV exposed persistently seronegative Kenyan female sex workers were shown to be associated with age and recent HIV-1 exposure, but not with protection against HIV-1 infection. The authors note that CTL may be the result of a non-productive HIV infection, but not mediate protection; alternatively, the low incidence, possibly due to behavioral interventions, may not give adequate sampling to detect the response.

**HXB2 Location** HIV-1

**Author Location**

**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Country** France**Keywords** HAART, ART, characterizing CD8+ T cells, immune dysfunction**References** Kryworuchko *et al.* 2004

- A subset of HIV-1 infected untreated patients had CD8+ T-cells that were unable to respond to IL-2 by activating STAT5a and b proteins. This was correlated with an impaired activation of the upstream kinase Jak-3. 6 months of HAART was shown to restore Jak/STAT signalling in those patients and their CD8+ T-cell response to IL-2. This suggests another mechanism for immune dysfunction in HIV infected patients.

**HXB2 Location** HIV-1**Author Location****Epitope****Subtype** A, B, C, D, F, G, U**Immunogen** computer prediction**Species (MHC)** human**Keywords** vaccine antigen design**References** Maksyutov *et al.* 2004

- Every HIV protein was shown to have some regions that were highly similar to the regions of human proteins. Most of those regions contained T-cell or/and B-cell epitopes. The epitopes shared by HIV and its host may have immunopathogenic potential through stimulating autoimmunity and should possibly be excluded from HIV vaccines. All HIV proteins from the sequence of BH10 were compared to human proteins, as well as many HIV-1 V3 variants.

**HXB2 Location** HIV-1**Author Location** (ELI)**Epitope****Immunogen** in vitro stimulation or selection**Species (MHC)** human**Assay type** Cytokine production, proliferation, Chromium-release assay, Flow cytometric T-cell cytokine assay**Keywords** class I down-regulation by Nef, rate of progression, dendritic cells, immune dysfunction**References** Quaranta *et al.* 2004

- Exogenous Nef protein activates immature DCs and inhibits the capacity of DCs to prime CD8+ T-cell responses by down-regulating their proliferation and function capacities. Nef induces CD8+ T-cell apoptosis by up-regulating TNF-alpha and FasL production by DCs, while DCs are protected from apoptosis themselves. These mechanisms, as well as by down regulation of the HLA class I proteins, can contribute to HIV-triggered immune dysfunction.

**HXB2 Location** HIV-1**Author Location****Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Country** Switzerland**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ **Keywords** rate of progression**References** Oxenius *et al.* 2004a

- In untreated, HIV-1 chronically infected patients, CD4+ T-cell responses and, to a lesser extent, CD8+ T-cell responses, were found to inversely correlate with disease progression rate. Polymorphisms in CCR genes, HLA genotype and GB virus C coinfection were not found to be related to slower disease progression.

**HXB2 Location** HIV-1**Author Location** (B clade)**Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Country** Canada**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** genital and mucosal immunity, characterizing CD8+ T cells**References** Sheth *et al.* 2004

- HIV viral load in semen is found to be 10-fold lower than in blood. No correlation was found between viral load in either semen or blood and systemic HIV-specific CD8 T-cell responses, in 20 samples.

**HXB2 Location** HIV-1**Author Location****Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* DNA with CMV promotor, virus-like particle (VLP), modified vaccinia Ankara (MVA) *Strain:* B clade *HIV component:* Env, Gag, Pol, Protease, RT**Species (MHC)** macaque**Assay type** T-cell Elispot, Intracellular cytokine staining**Keywords** vaccine antigen design**References** Smith *et al.* 2004

- Macaques were immunized with codon-optimized Gag DNA and non-codon-optimized Gag-Pol-Env DNA vaccines, expressed as VLPs as aggregates, followed by an MVA boost. There was no significant difference in anti-Gag T-cell responses and anti-Env Ab responses between the different vaccines. A second MVA boost did not increase T-cell responses but it increased anti-Env Ab titers by 40- to 90-fold.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen****Species (MHC)** human**Keywords** review, epitope processing, rate of progression, escape, early-expressed proteins, vaccine antigen design**References** Yang 2004

- This review considers CTL biology in HIV infection in the context of vaccine design principles. Since HIV-1 infection damages immunity through depletion of CD4+ T-cells, which in turn results in diminished capacity of the immune system to produce new and functional CTL responses, maximizing the breadth of CTL responses might not be enough for an HIV-1 vaccine. CTLs recognizing early proteins might be more prone to epitope escape mutation, while those recognizing more conserved structural proteins might be more likely to persist, so focusing on more conserved proteins those might be a good strategy to produce an attenuating vaccine.
- Original antigenic sin is discussed, the initial responses to an antigen that persist even after escape occurs, blunting the later immune response. If the goal is to prevent disease, focusing on conserved late expressed proteins might be the best target, where the fitness cost is greatest for escape; if the goal is to prevent infection, focusing the vaccine on the more variable early expressed proteins that elicit the first responses, Tat and Nef, might be best.

**HXB2 Location** HIV-1**Author Location** p24 (HIV-2 ROD, HIV-1 IIIB)**Epitope****Subtype** B, HIV-2**Immunogen** HIV-1 or HIV-2 infection**Species (MHC)** human**Country** Gambia**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** rate of progression, HIV-2**References** Jaye *et al.* 2004

- A comparison of T cell responses in HIV-1 and HIV-2 infected asymptomatic patients with CD4+ cell counts 20% showed no significant difference between groups. Viral loads were roughly 20 times greater in HIV-1 positive patients than HIV-2 positive patients.
- 10/20 (50%) of HIV-1 infected patients demonstrated proliferative responses with SI greater than 1.4 to gp120, and 11/20 to p24. 8/29 (29%) of HIV-2 infected patients recognized gp105, and 8/29 (29%) p26. Cytokine responses in both groups did not differ.
- 9/21 (43%) of HIV-1 + and 15/30 (50%) of HIV-2 + patients had cytotoxic T cell responses to Gag, and 3/21 (14%) HIV-1 + and 8/30 (27%) HIV-2 + responded to Pol.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Country** Spain**Assay type** proliferation, Intracellular cytokine staining**Keywords** HAART, ART**References** López *et al.* 2004

- A clinical trial compared chronically HIV-1 infected patients who had replaced HAART with didanosine (ddI) and hyroxurea (HU) were followed for 12 months to an untreated HIV+ group and a group that continued on HAART.

- Approximately 20% of the patients treated with ddI-HU had detectable CD4+ T-cell proliferative responses to Gag and Env in contrast to drug-naive and HAART treated HIV-infected patients, who had few or no responses.
- HIV-specific CD8+ T-cell responses were higher in ddI-HU treated patients than HAART treated patients, even in individuals that maintained undetectable viral loads.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen****Species (MHC)****Keywords** review, adjuvant comparison**References** Mitchison & Sattentau 2005

- Review summarizes mechanisms of immunoregulation relevant for new vaccine development, with a brief summary of adjuvant triggering innate immunity through Toll-like receptors (TLRs), Nod molecules, and other activators. DNA encoded adjuvants that have been tested in DNA vaccines are summarized. The balance between Th1 (CTL activating) and Th2 (B cell activating) responses is discussed, and it is noted that BALB/c mice are predominately Th2 responders, C57BL Th1.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** escape**References** Piontkivska & Hughes 2006

- Greatest amino acid diversity is found in sites in the HIV genome that are spanned by antibody epitopes. Sites spanned by CTL epitopes, but not by antibody epitopes, showed reduced amino acid diversity, even in comparison to non-epitope sites. However, mutations within CTL epitopes were more likely to be convergent than mutations within antibody epitopes. These patterns were consistent both in Gag and in Env.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD8 T-cell RecycleSpot - IFN $\gamma$ **Keywords** assay standardization/improvement, optimal epitope**References** Bihl *et al.* 2005

- This study describes a novel approach to achieve maximal information from an extensive set of antigens (HIV, EBV, CMV, HCV, and HBV) to determine the magnitude of T-cell responses while requiring minimal cell numbers. Large sets of peptides based on optimally defined epitopes from each pathogen are used. It is shown that, when compared to ex vivo cell preparations, antigen-unspecific in vitro T-cell expansion maintains the breadth of detectable T-cell responses. Also, harvesting cells from negative ELISpot wells for re-use (RecycleSpot) maximizes the use of available cells.

- HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** genital and mucosal immunity, characterizing CD8+ T cells  
**References** Ibarrondo *et al.* 2005
- The breadth and magnitude of HIV-1-specific CTL responses in blood and sigmoid colon mucosa were assessed in 16 patients. The magnitude of pool-specific CTL responses in blood and mucosa was correlated within each individual and across all individuals. CTL targeting was also found to correlate between these 2 compartments, with Nef being the most highly targeted region, followed by Gag. No correlation between the magnitude and breadth of CTL responses and viremia and blood CD4 levels was found in any of the compartments. Concordant peptide pool responses were found in the blood and mucosa 85%; pools that differed were near the threshold of detection.
  - This study suggests that HIV-1-specific CTL responses in the blood mirror those in the mucosa during chronic infection.

- HXB2 Location** HIV-1  
**Author Location** (Z321)  
**Epitope**  
**Subtype** A, B, C, G  
**Immunogen** vaccine  
*Vector/Type:* gp120 depleted whole killed virus  
*Strain:* AG recombinant HZ321  
*HIV component:* gp120 depleted virus  
*Adjuvant:* CpG immunostimulatory sequence (ISS)  
**Species (MHC)** mouse  
**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons, genital and mucosal immunity, adjuvant comparison, vaccine antigen design, characterizing CD8+ T cells  
**References** Jiang *et al.* 2005
- Mice were given intranasal immunization with inactivated gp120-depleted HIV-1 antigen plus a CpG ODN adjuvant and examined for local immune responses in the genital tract. Mice immunized with HIV Ag plus CpG produced significantly higher levels of IFN-gamma and beta-chemokines than mice immunized with Ag alone, and their lymphocytes showed significant HIV-specific proliferation. CD8 T-cells were increased in the genital tracts of mice immunized with HIV Ag plus CpG.
  - The vaccine antigen Z321 is clade G in Gag. Cross-clade protection against an intravaginal challenge was observed for clades A, C, and G, but not clade B.

- HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** computer prediction  
**Species (MHC)** human

- Assay type** Other  
**Keywords** assay standardization/improvement, computational epitope prediction  
**References** Larsen *et al.* 2005

- A computational epitope identification method integrating predictions of MHC class I binding affinity, TAP transport efficiency and C-terminal proteasomal cleavage was compared to two already existing computational epitope identification tools. It was shown that the new ANN method performed better, reducing the number of nonamers needed to be tested in order to identify 85% of the epitopes from 9-10% to only 7%.

- HXB2 Location** HIV-1  
**Author Location** (A, B, and C consensus)  
**Epitope**  
**Subtype** A, B, C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons  
**References** Yu *et al.* 2005

- HIV-specific T-cell responses to peptide from A, B, and C clade spanning the entire HIV proteome were assessed in clade B infected individuals. Many cross-reactive responses were observed against clade A, B, and C consensus sequences, preferentially recognized in conserved regions with low intra-clade diversity and high inter-clade homology.
- At the individual peptide level, within clade responses to B clade peptides were more frequent. 194 responses were detected with only one peptide, of these 105 recognized B clade, 55 C clade, and 34 A clade. 125 responses recognized peptides from two clades, and 110 of these were with B plus either A or C. 166 responses were cross-reactive with all three clades.

- HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** computer prediction  
**Species (MHC)**  
**Keywords** escape, viral fitness and reversion  
**References** Gansov & De Boer 2006

- A simple mathematical model is used to estimate costs of CTL escape mutations and killing rate of CTLs. Using in vivo data, it is shown that minimal estimates of the fitness cost of the escape mutations and minimal estimates of the average killing rate can be obtained. This general model may be used for both acute and chronic phases of SIV/HIV infection.
- Fitness cost is found to be proportional to the rate of replacement of the mutant by wild-type rather than the time taken for this to happen. Exponential growth of the virus is assumed during such reversion experiments. However, no virus growth is assumed during escape experiments to gauge the minimum average rate at which the CTL response clears one viral epitope.

- HXB2 Location** HIV-1  
**Author Location**  
**Epitope**

**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** review, escape**References** Frahm & Brander 2007

- This report characterizes HIV epitope variants with a view to guiding vaccine design. It discusses immune correlates of controlled HIV infection, HIV escape from cellular immunity and the effects of sequence diversity on T-cell recognition.
- In controlled infections it is noted that diversity of HIV-specific cells is associated with better control of infection than magnitude of HIV-specific response. The specific epitopic region targeted by host immune cells is a determinant in controlling infection too. However, high avidity responses are effective in virus control and epitope recognition despite a limited T-cell receptor repertoire. While HLA-B alleles mediate most CTL cellular immunity, subdominant responses are key in effective immune control. On the other hand, uncontrolled virus replication is linked to high expression of PD-1, low IL-7R, fewer early and intermediate differentiated cells, absence of CD4 T-cell help and reduced proliferation.
- HIV escape can occur on several fronts - viruses may develop compensatory changes to restore fitness; transmission between individuals with different HLA types allows virus reversion; certain epitopes may disappear from circulating viral populations if there is a high population frequency of specific HLA and specific epitope variants can even act as antagonists or partial agonists either silencing total epitopic T-cell responses or inducing immune responses even with only partial functionality.
- Sequence diversity is greatly increased by the spread of unique recombinant forms of HIV in individuals. The authors advise the use of detailed single-peptide-based analyses in addition to using peptide pools. They also suggest 3 approaches to incorporating sequence diversity in vaccine studies.

**HXB2 Location** HIV-1**Author Location****Epitope****Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A\*01, A\*02, B\*08, B\*40, Cw\*03, Cw\*07; A\*01, A\*31, B\*08, B\*35, Cw\*04, Cw\*07; A\*02, A\*24**Country** Australia**Assay type** Other**Keywords** acute/early infection, immune evasion, viral fitness and reversion**References** Li *et al.* 2007

- To address the role of reversions in early HIV-1 evolution, the authors studied 7 acute infected AIDS patients longitudinally. Their findings show that most forward mutations in HIV-1 were significantly likely to occur within and including "neighboring" CTL epitope residues restricted by the host's HLA type. 62% of early/fast mutations arising within 6 months of infection were reversions to consensus sequences while 73% of forward mutations occurred as late/slow mutations. Almost 30% of reversions were found in CTL epitopes not restricted by the current host. Reversions themselves occurred faster in conserved residues as well as more conserved proteins like

Gag and Pol; however slow reversions were seen more frequently in Env and non-structural proteins like Vif, Tat and Nef. The authors suggest that fitness cost and structural constraints may be the underlying cause for high and early reversion rates.

**HXB2 Location** HIV-1**Author Location****Epitope****Subtype** B, C**Immunogen** vaccine*Strain:* A clade, B clade *HIV component:* Env, Gag, gp120, Nef, Pol, Rev, Tat, Vif, Vpr, Vpu**Species (MHC)** human**Assay type** Other**Keywords** vaccine antigen design**References** Fischer *et al.* 2007

- In order to work towards a global vaccine covering multiple variable and conserved epitopes, the authors have designed a method for generating polyvalent vaccines optimized against HIV-1 M group viruses. 4 mosaic proteins were produced by in silico recombination natural sequences, including common, and excluding rare potential 9-mer epitopes. Total coverage was assessed by tracking exact and partial 9-mer matches. Such mosaic, polyvalent multi-antigens that resemble a native protein would also allow more natural delivery and epitope processing in vivo.

**HXB2 Location** HIV-1**Author Location** (HXB2)**Epitope****Subtype** B**Immunogen** HIV-1 infection, SIV infection, SHIV infection**Species (MHC)** human, macaque**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other**Keywords** assay standardization/improvement, escape, immune evasion, viral fitness and reversion**References** Asquith & McLean 2007

- By using a method developed recently [Asquith *et al.*, PLOS Biology. Vol:4, Issue: 4. pp. 583-592 (2006)] for estimating the in vivo rate at which CTLs kill HIV-1-productively infected cells, the authors compare previously determined human CTL control of HIV-1 infection with macaque CTL control of SHIV/SIV infection. Quantitatively, it was shown that macaque CTLs kill infected cells significantly faster than human. Also, in most cases for both species, the outgrowth of escape variants was too rapid to put anything but a lower bound on the escape rate. There was also no significant difference in virus escape rate between macaque chronic or acute infection.
- In spite of the fact that CTL response in macaques is faster than in humans, CTL-induced viral escape variants appeared more rapidly in macaques than in humans. However, macaque escape variants also had a higher fitness cost, as evidenced by their higher rate of reversion upon transfer of viral variant to macaques that did not present the HLA restricting the epitope under study. Taken together, it was determined that immunodeficient virus-infected cells were killed almost 10 times more rapidly in macaques than in humans.

**HXB2 Location** HIV-1  
**Author Location** (HXB2)  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* DNA, adenovirus type 5 (Ad5), DNA prime with Ad5 boost *Strain:* B clade  
*HIV component:* Gag, Nef, Pol

**Species (MHC)** human  
**Country** Brazil, Botswana, Cameroon, Malawi, United States, South Africa  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** assay standardization/improvement  
**References** Dubey *et al.* 2007

- To evaluate the immunogenicity of various vaccine modalities the IFN-gamma ELISpot assay is optimized and validated here across vaccine recipients and regimens, using 9-, 15- or 20-mer peptide pools. An empirical method to establish positivity criteria with a <1% false-positive rate was established at  $\geq 55$  spots/ $10^6$  PBMCs and  $\geq 4$ -fold over mock negative control. Moreover, 15-mer peptides had greater sensitivity than 20-mers as well as a greater specificity; i.e. ability to stimulate CD4 and CD8 T cells with fewer false-positives and cross-reactive responses, than 9-mers.

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** assay standardization/improvement, immunodominance  
**References** Fu *et al.* 2007

- Using IFN-gamma ELISpot analyses and peptide pools, the authors studied a cohort of 54 chronically infected HIV-positive individuals to evaluate CTL responses against HIV-1. 2 criteria were established to score an ELISpot as positive - a reading of  $> 55$  SFC/ $10^6$  PBMC and an antigen response at least 4-fold higher than that of mock antigen. By performing T subset depletion the contribution of CTL responses to cellular immunity was proven. These CTL immune responses were mounted mostly against Gag, Pol and Nef peptide pools, and to a lower extent versus Rev and Tat peptides. Without antiviral therapy, host CTL responses correlate directly with plasma viral loads during chronic infection.

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** South Africa  
**Assay type** Intracellular cytokine staining  
**Keywords** assay standardization/improvement  
**References** Meddows-Taylor *et al.* 2007

- A whole blood peptide mapping intracellular cytokine staining assay was developed, that allows the direct comparison, at individual peptide level, of CD4+ and CD8+ T cell responses. This assay also allows to monitor the responding cell type in the same reaction and requires considerably less blood than would be necessary if PBMC were first isolated prior to peptide stimulation.
- 396 overlapping peptides across Gag, Pol, Nef, Env, Tat, Rev, Vif, Vpu, Vpr were tested. CD8+ responses were higher in magnitude and in frequency than CD4+ responses in HIV patients screened by this method.

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* lipopeptide *Strain:* B clade consensus, B clade LAI *HIV component:* Gag, gp120, Nef

**Species (MHC)** human  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$   
**Keywords** vaccine-induced epitopes, therapeutic vaccine  
**References** Gahery *et al.* 2006

- This study describes CD4+ and CD8+ T cell responses detected before and after immunization with a mixture of lipopeptides in chronically infected patients treated by HAART. Lipopeptides induces multiple new responses and thus could be used a new immunotherapy strategy.

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** Other  
**Keywords** immunodominance, escape, immune evasion, viral fitness and reversion  
**References** Rolland *et al.* 2007a

- This correspondence is in response to an article by Arien *et al.* (2007) Nature Reviews Microbiology 5(2):141-51. Here the authors claim that in silico studies demonstrate HIV follows "survival of the flattest" effects. They propose that HIV-1 shifts to robust population characters that protect it from niche perturbations and increase its survival at the expense of replicative fitness. The balance between intra-host replication and inter-host transmission is suggested to be held by circulating viruses going from high fitness and low mutational support to lower fitness and high mutations. They maintain that lower fitness does not equal virus attenuation as discussed by Arien *et al.*

**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human



**Keywords** vaccine-specific epitope characteristics, immunodominance, escape, vaccine antigen design, immune evasion, neutralization

**References** Rolland *et al.* 2007c

- To sidestep the issue that in vaccine design against AIDS, providing protection against global diversity may be an insurmountable problem, a prototype conserved elements (CE) vaccine comprising 45 8-residue long HIV segments is described. Therefore the authors seek to cope with HIV-1 diversity by avoiding it altogether. Stringent conservation criteria are followed to find CEs devoid of mutable segments across M group viral proteomes. Most CE were identified in Pol, Gag, Env, Vif and Rev. Even though most CE peptides were identified in Pol, these are rarely targeted in natural infections probably because of the much lower ratio of Pol proteins produced compared to Gag. Therefore Pol CE were used here in contrast to most other vaccines. Similarly, Nef was not used and fewer Env CE peptides were used in this vaccine, even though they are usually found in other vaccines. Many CE segments contained known CTL epitopes and are implicated with LTNPs. One crucial advantage of this strategy is that a single global CE vaccine should work against all circulating HIV-1 M strains.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen**

**Species (MHC)**

**Keywords** review

**References** Mullins & Jensen 2006

- This is a review discussing HIV mutational potential and perspective for effective vaccines.

**HXB2 Location** HIV-1

**Author Location** Rev (B clade consensus)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection, SHIV infection

**Species (MHC)** macaque

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** assay standardization/improvement

**References** Chea *et al.* 2005

- The study describes a novel in vivo killing (IVK) assay using overlapping peptide pools pulsed onto autologous fluorescently labeled PBMC. Analysis of SIV/HIV specific immunity in several weeks following JVK assays showed a marked enhancement of virus-specific CD8 and CD4 T-cell immunity.

**HXB2 Location** HIV-1

**Author Location** Env (MN)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection, SHIV infection

**Species (MHC)** macaque

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** assay standardization/improvement

**References** Chea *et al.* 2005

- The study describes a novel in vivo killing (IVK) assay using overlapping peptide pools pulsed onto autologous fluorescently labeled PBMC. Analysis of SIV/HIV specific immunity in several weeks following JVK assays showed a marked enhancement of virus-specific CD8 and CD4 T-cell immunity.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Malawi, South Africa, Zambia, Zimbabwe

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Other

**Keywords** subtype comparisons, escape, optimal epitope, HLA associated polymorphism

**References** Ngandu *et al.* 2007

- For HIV-1 subtype C, it is found that Nef and p24 peptides recognized by CTL response are usually conserved but p17 epitopes are highly variable. Also, database information for subtype C epitopes is severely lacking in comparison with subtype B.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human

**Assay type** Other

**Keywords** vaccine antigen design, immune evasion, optimal epitope

**References** Nickle *et al.* 2007

- To develop vaccines that include antigens versus circulating variation in consensus sequences as well as versus mutations, a computational method was developed to reconstruct ancestral sequence at the center of phylogenetic tree using 169 subjects' sequences. Also, to compass sufficient antigenicity, more antigenic sequences would be required, but to avoid large, full-length antigens, short protein sequences present at high frequencies in HIV-1 populations were used in constructs. In this study, 3 constructs were directed against highly variable Nef and immunologically important but conserved Gag. 82% 9-mer coverage for Gag and 62% for Nef were achieved.

CTL CD8+

## II-C

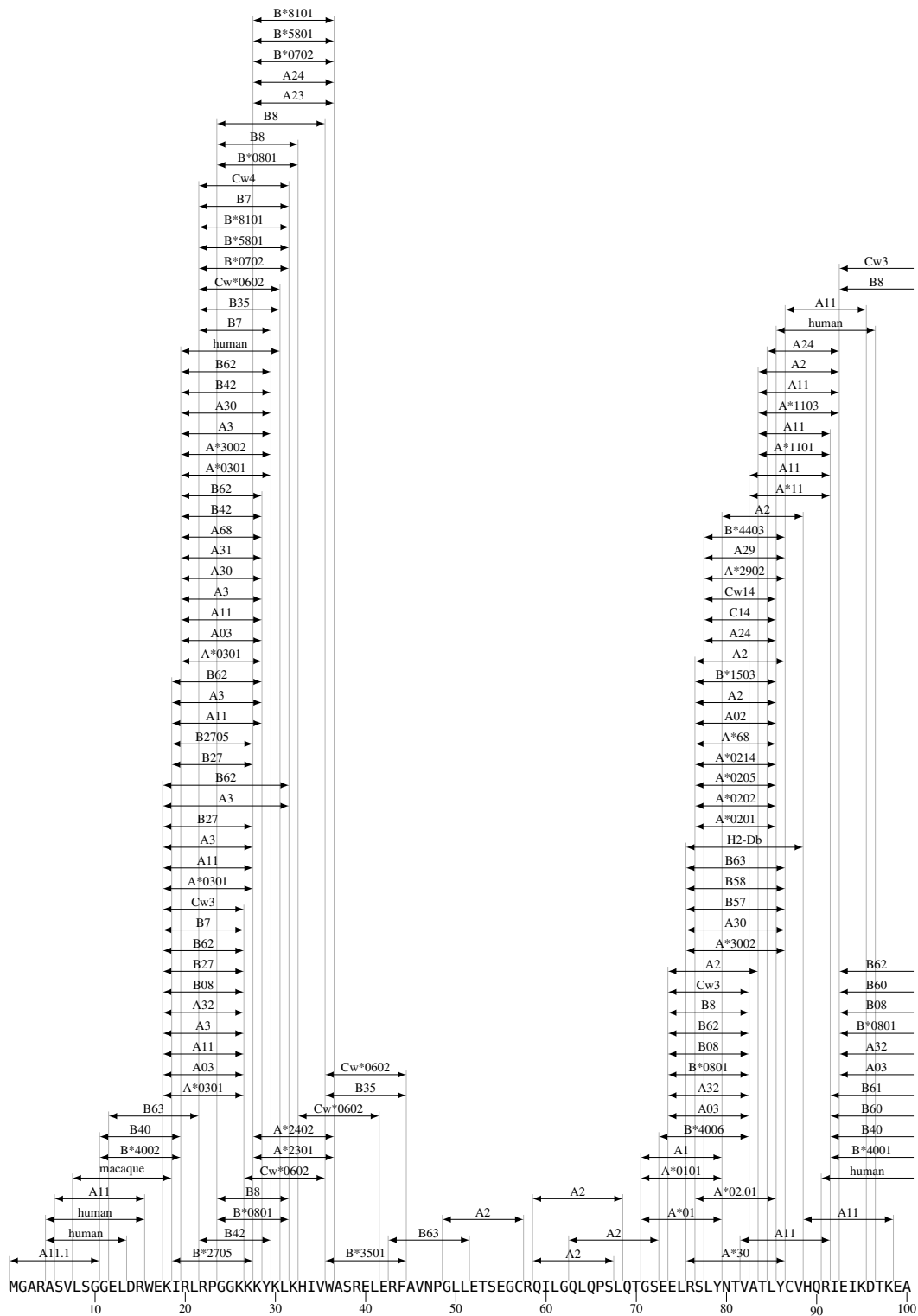
# Maps of CTL/CD8+ Epitope Locations Plotted by Protein

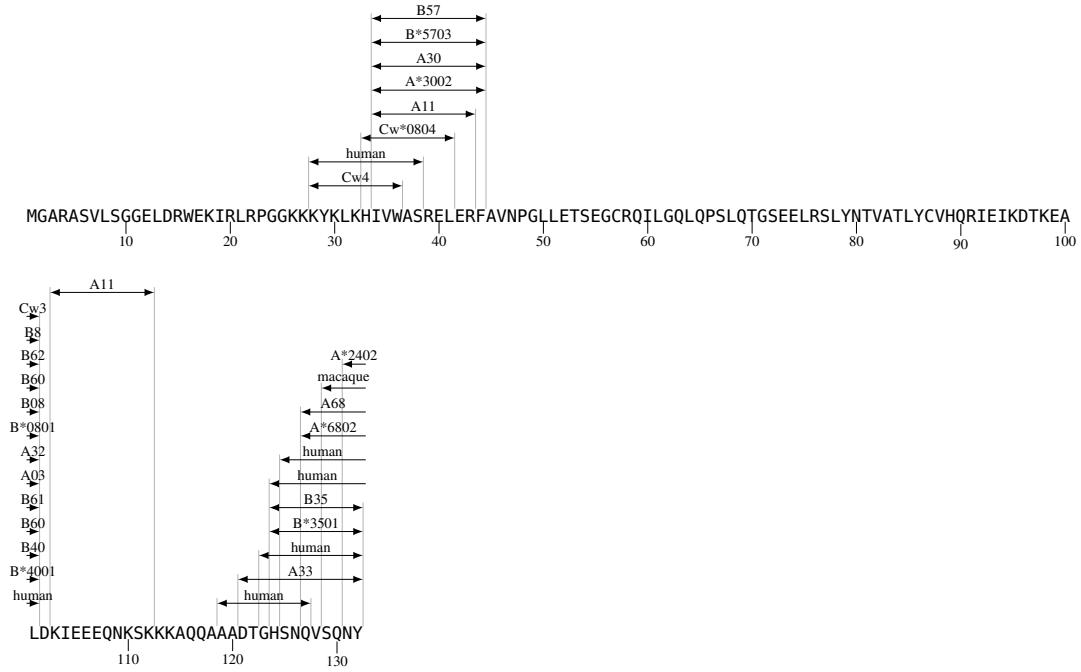
Linear CTL epitopes mapped to within a region of 14 amino acids or less are shown.

CTL CD8+

II-C-1 p17 CTL/CD8+ Epitope Map

CTL CD8+

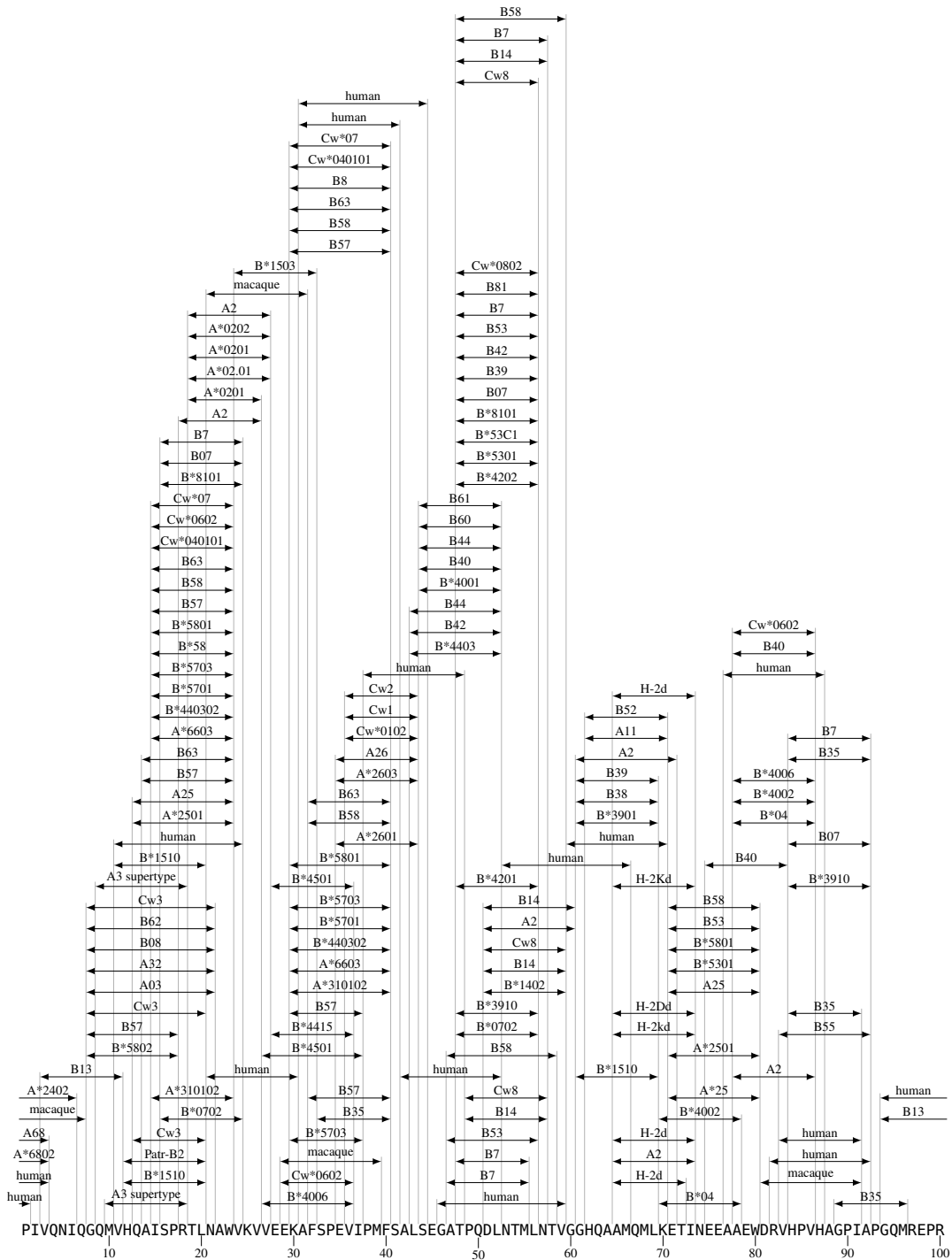


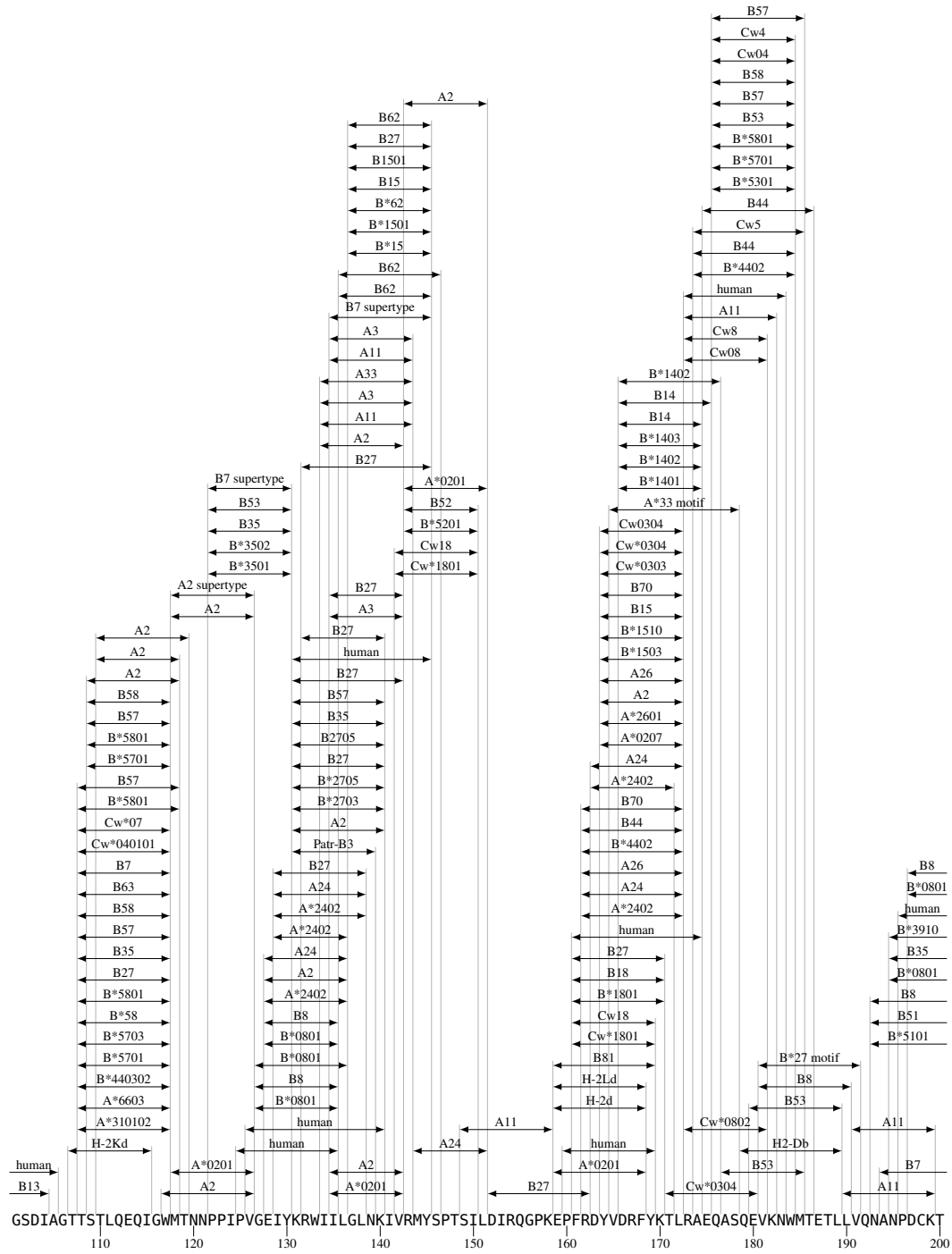


CTL CD8+

II-C-2 p24 CTL/CD8+ Epitope Map

CTL CD8+



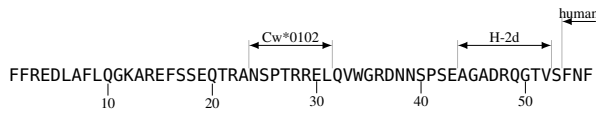


CTL CD8+

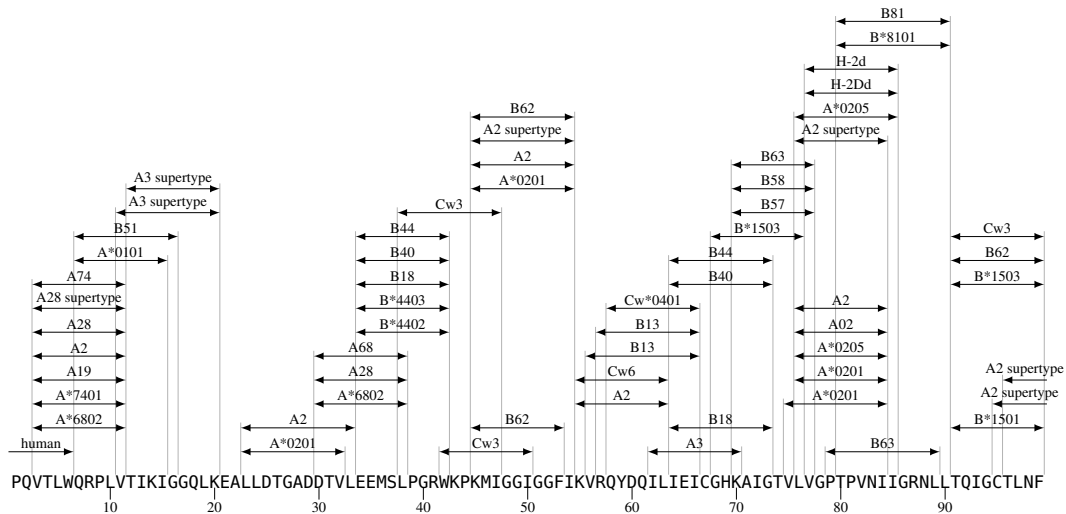




II-C-4 Gag/Pol TF CTL/CD8+ Epitope Map

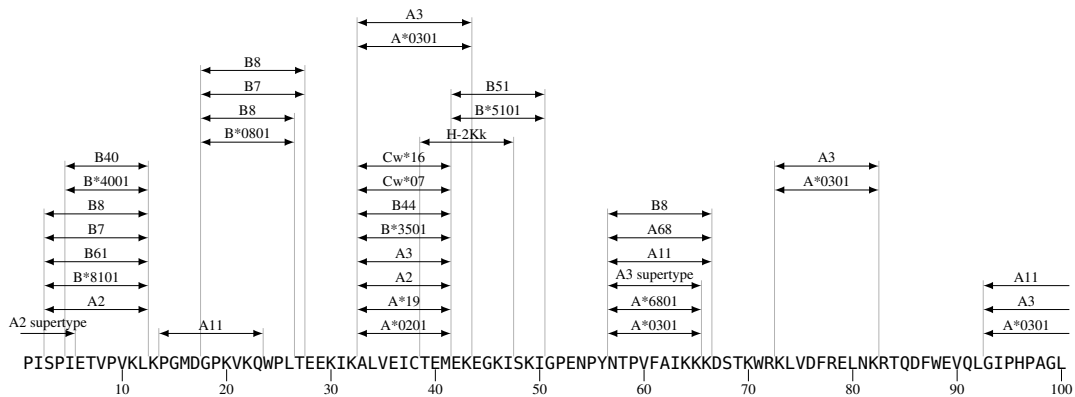


II-C-5 Protease CTL/CD8+ Epitope Map

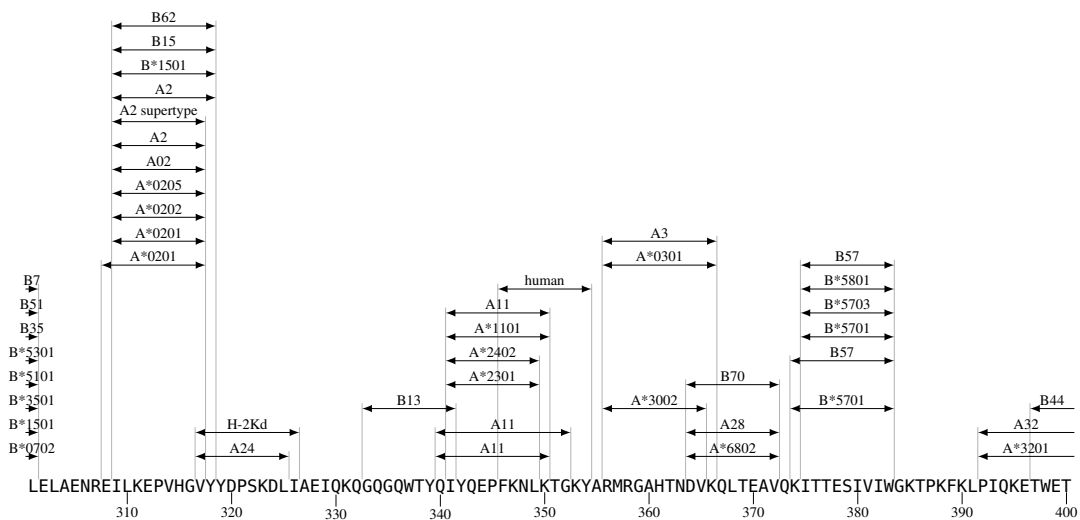
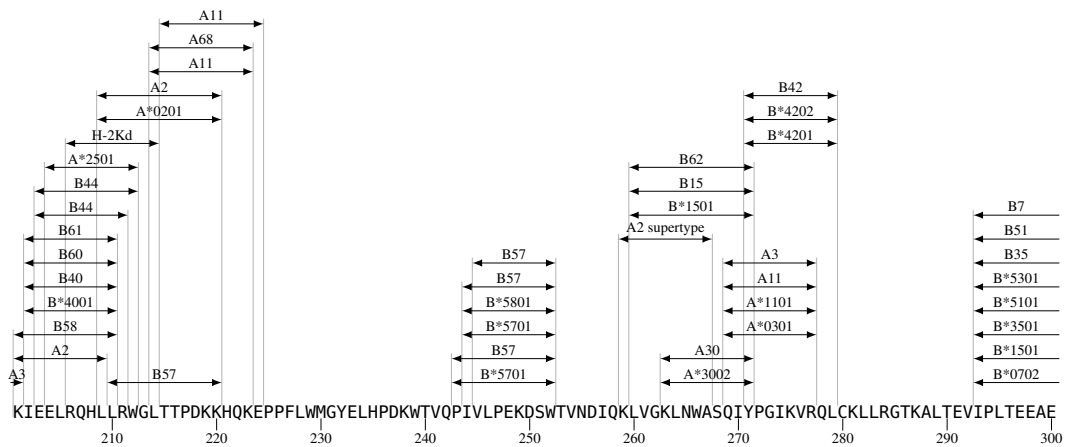
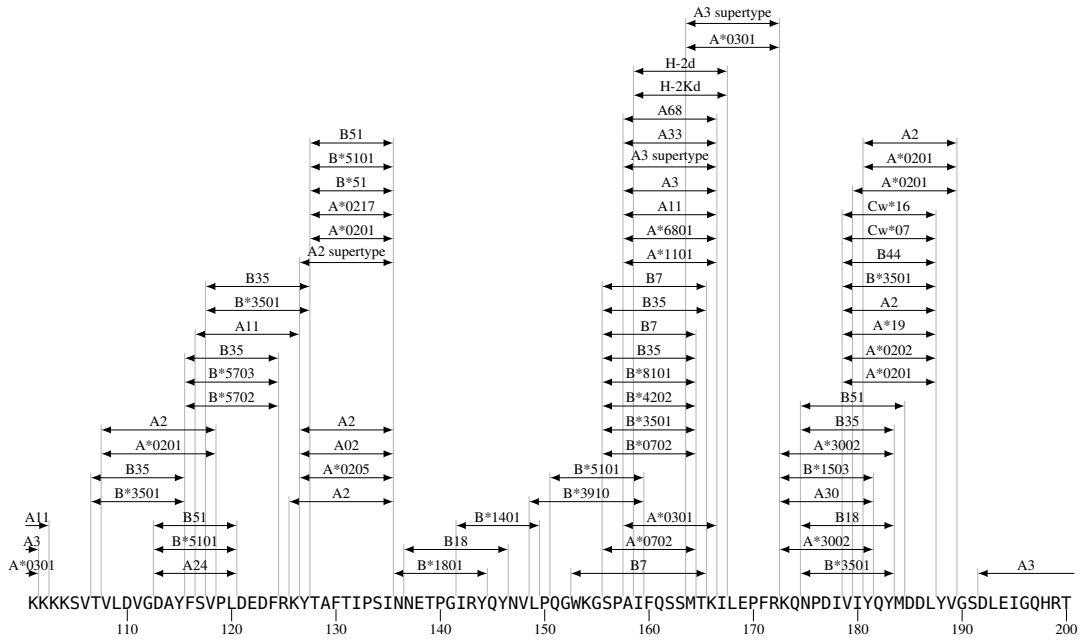


CTL CD8+

II-C-6 RT CTL/CD8+ Epitope Map



CTL CD8+



## Integrase CTL/CD8+ Epitope Map

## Maps of CTL/CD8+ Epitope Locations Plotted by Protein

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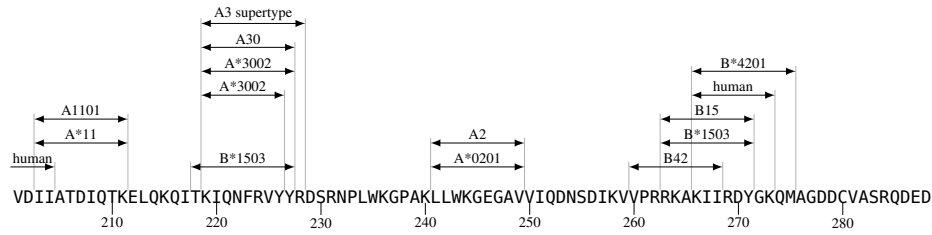
YALGIQAQPDQSESELVNOIIEQLIKKEKVYLAWVPAHKGIGGNEQVDKLVSAQIRKVL

CTL CD8+

## II-C-7 Integrase CTL/CD8 + Epitope Map

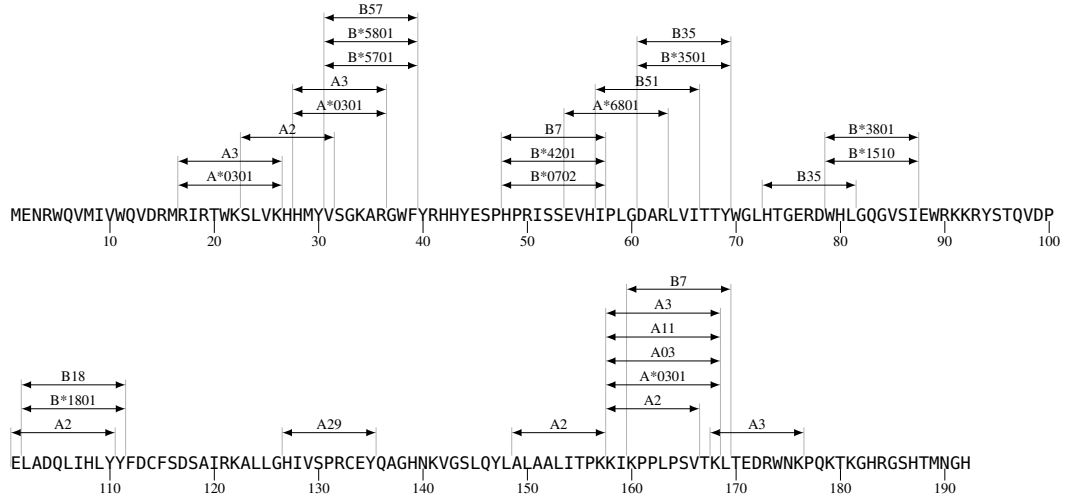
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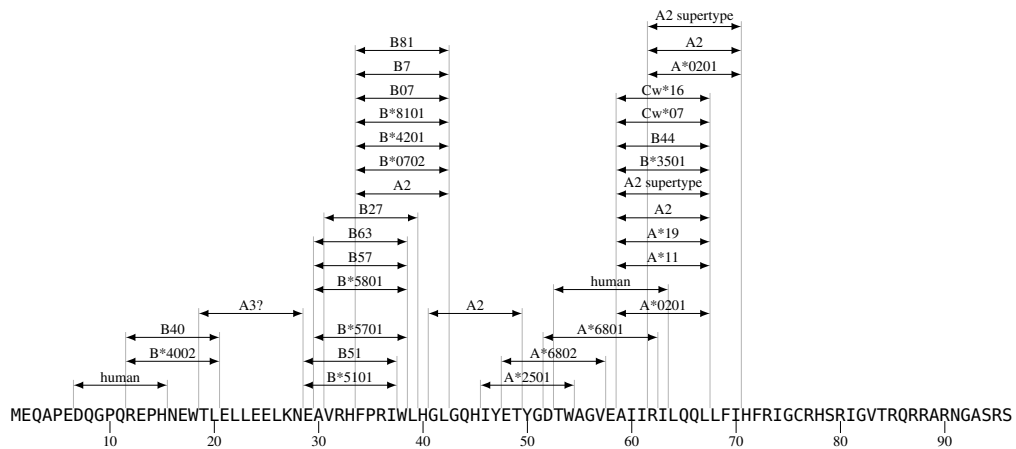


II-C-8 Vif CTL/CD8+ Epitope Map

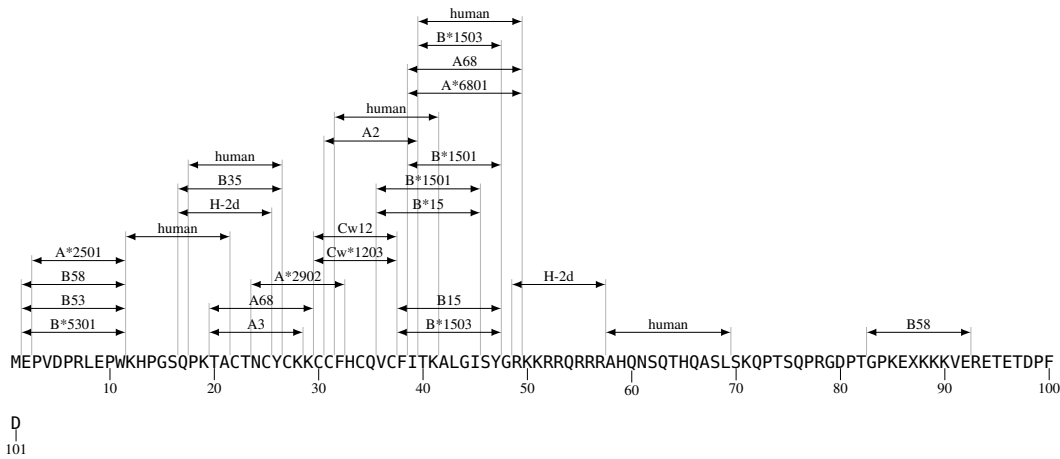
CTL CD8+



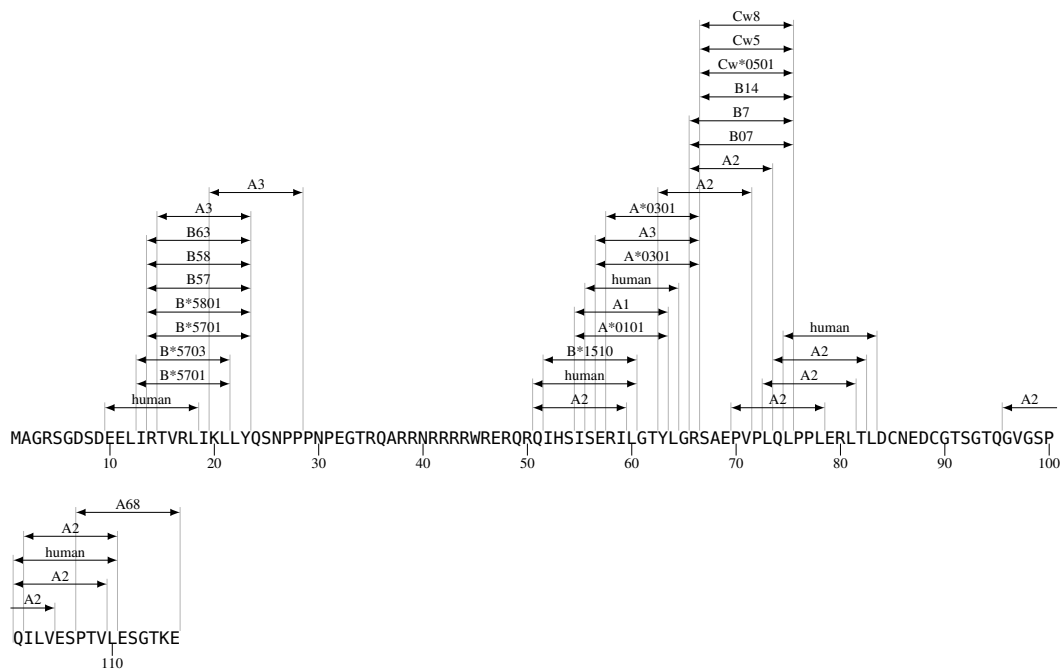
II-C-9 Vpr CTL/CD8+ Epitope Map



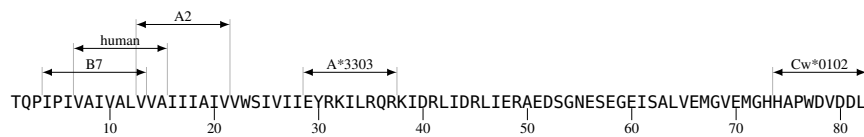
II-C-10 Tat CTL/CD8+ Epitope Map



II-C-11 Rev CTL/CD8+ Epitope Map



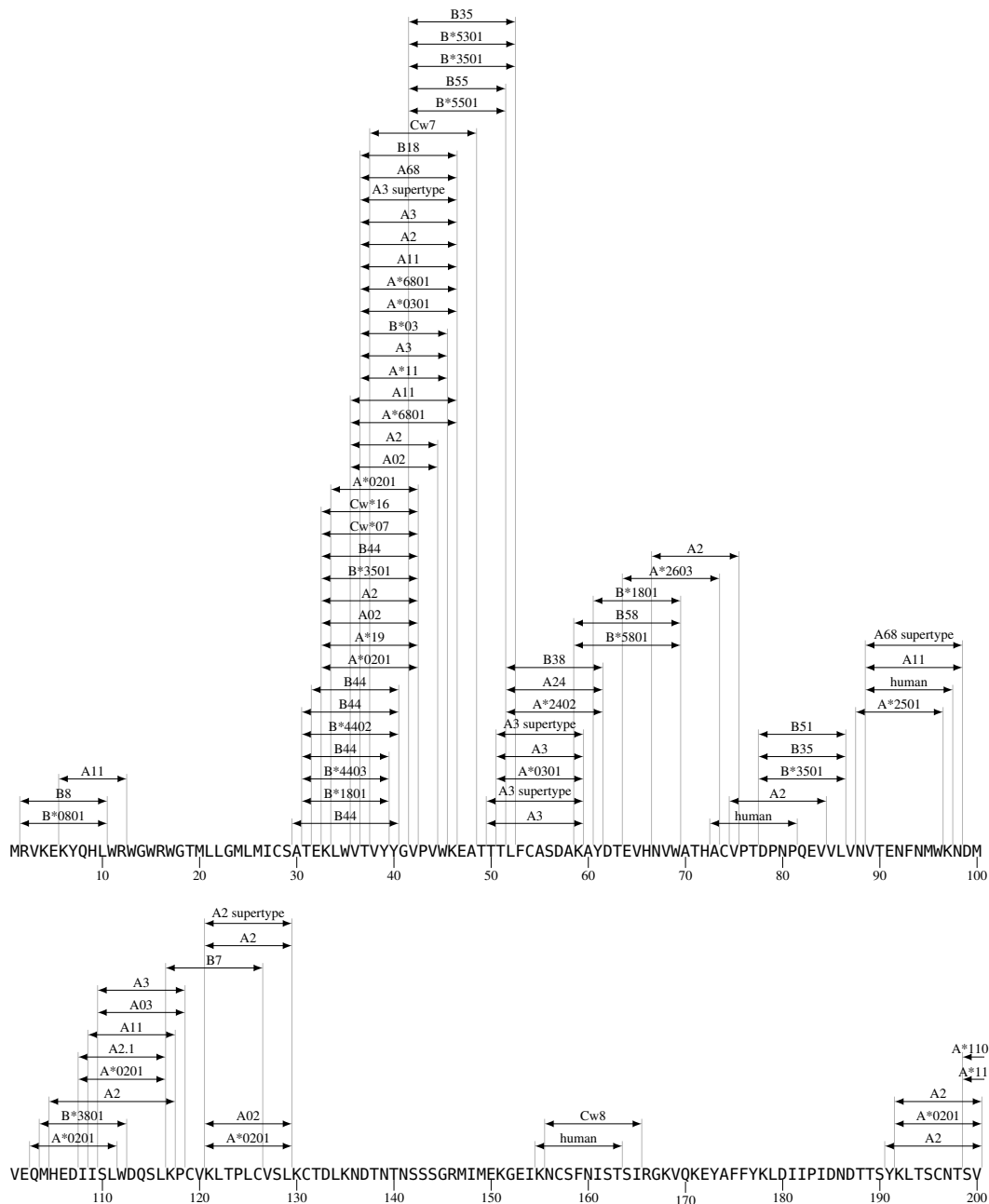
II-C-12 Vpu CTL/CD8+ Epitope Map

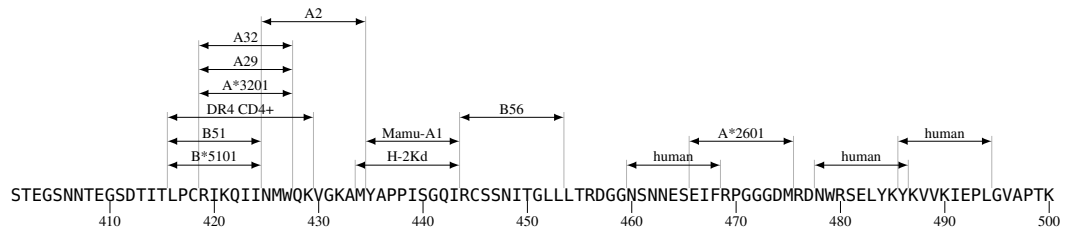
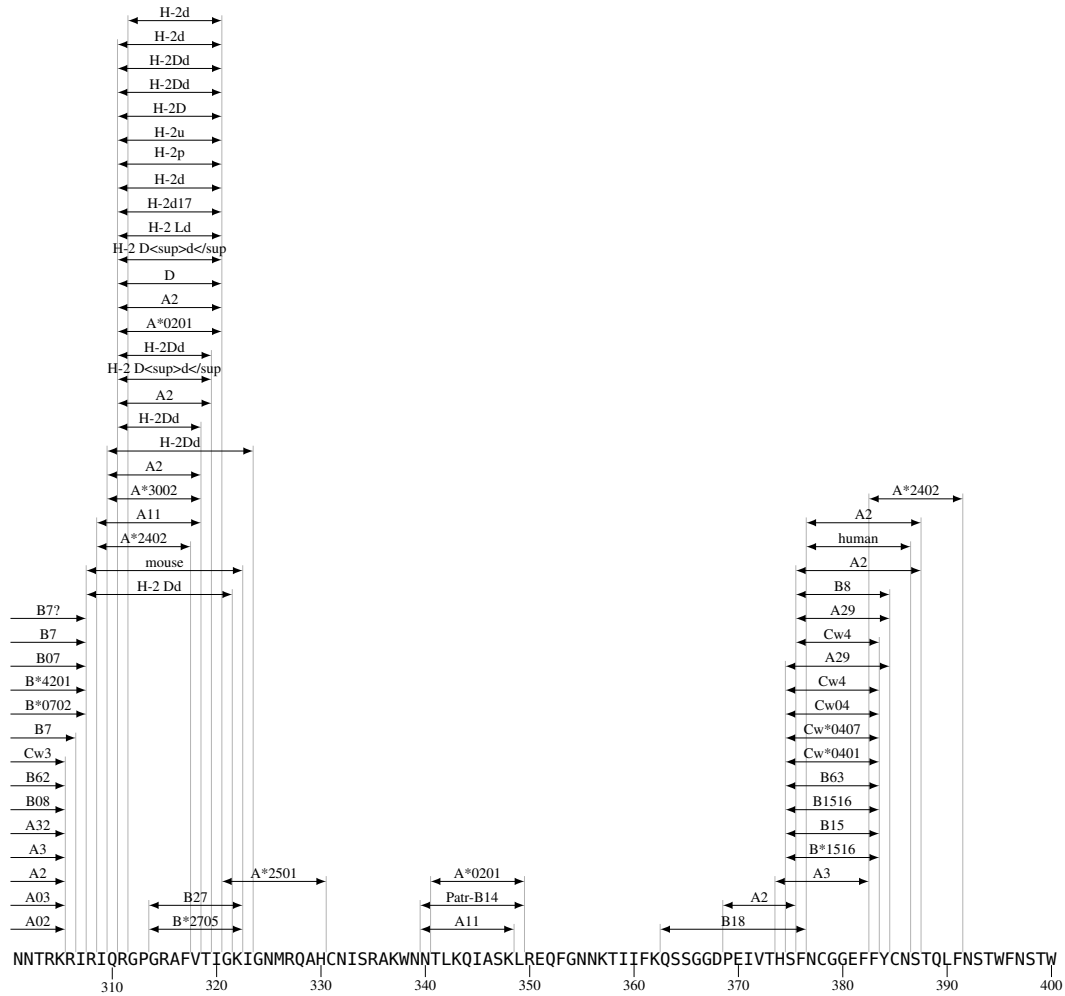
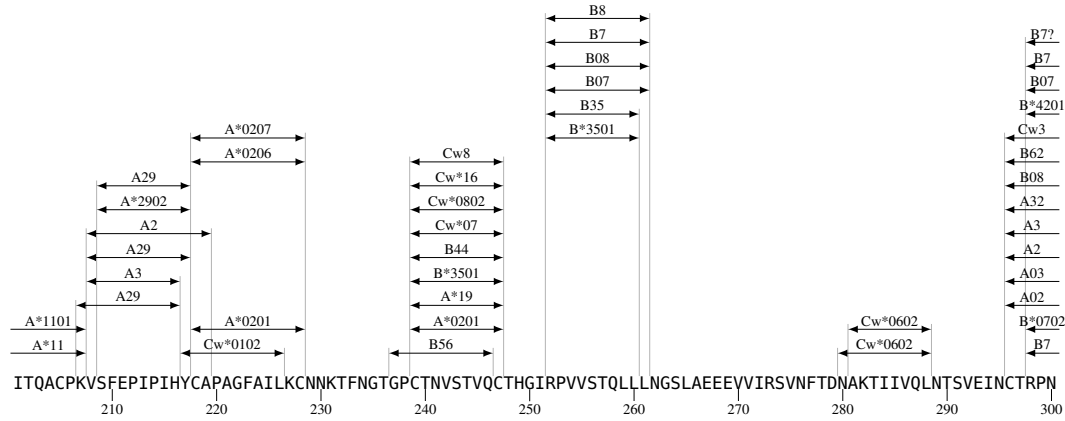


CTL CD8+

II-C-13 gp160 CTL/CD8+ Epitope Map

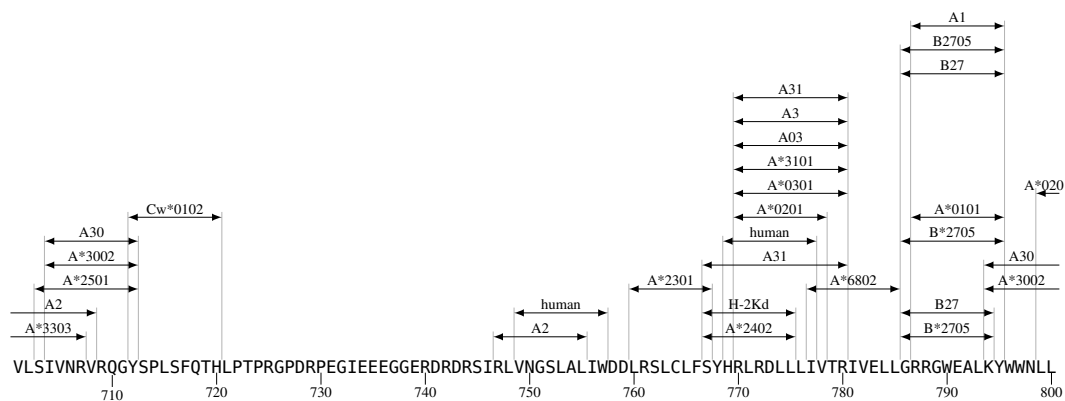
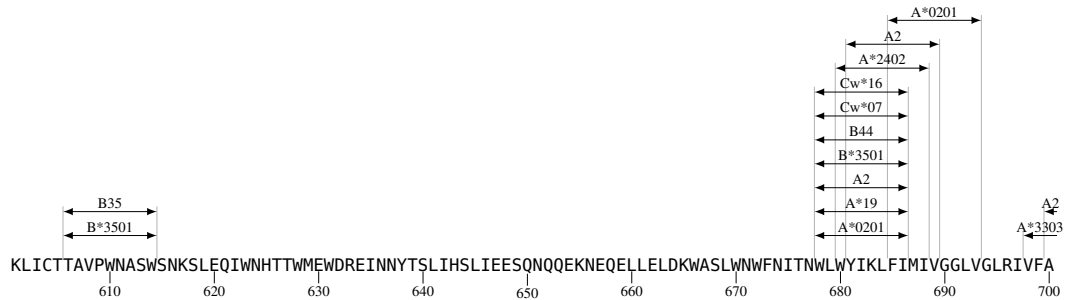
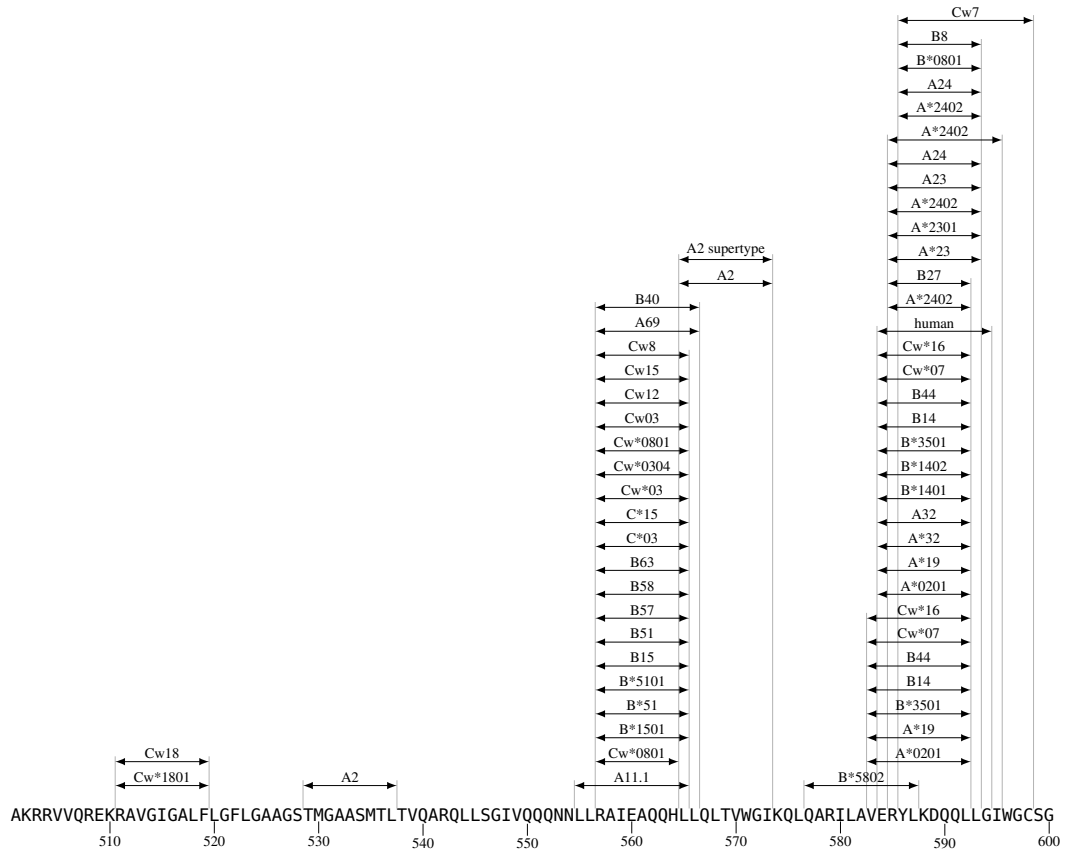
CTL CD8+



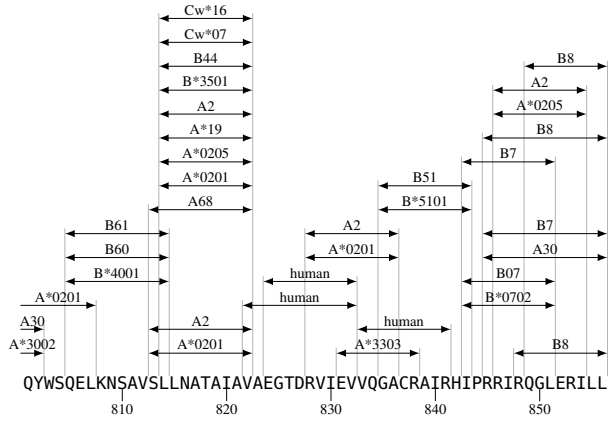


CTL CD8+

CTL CD8+



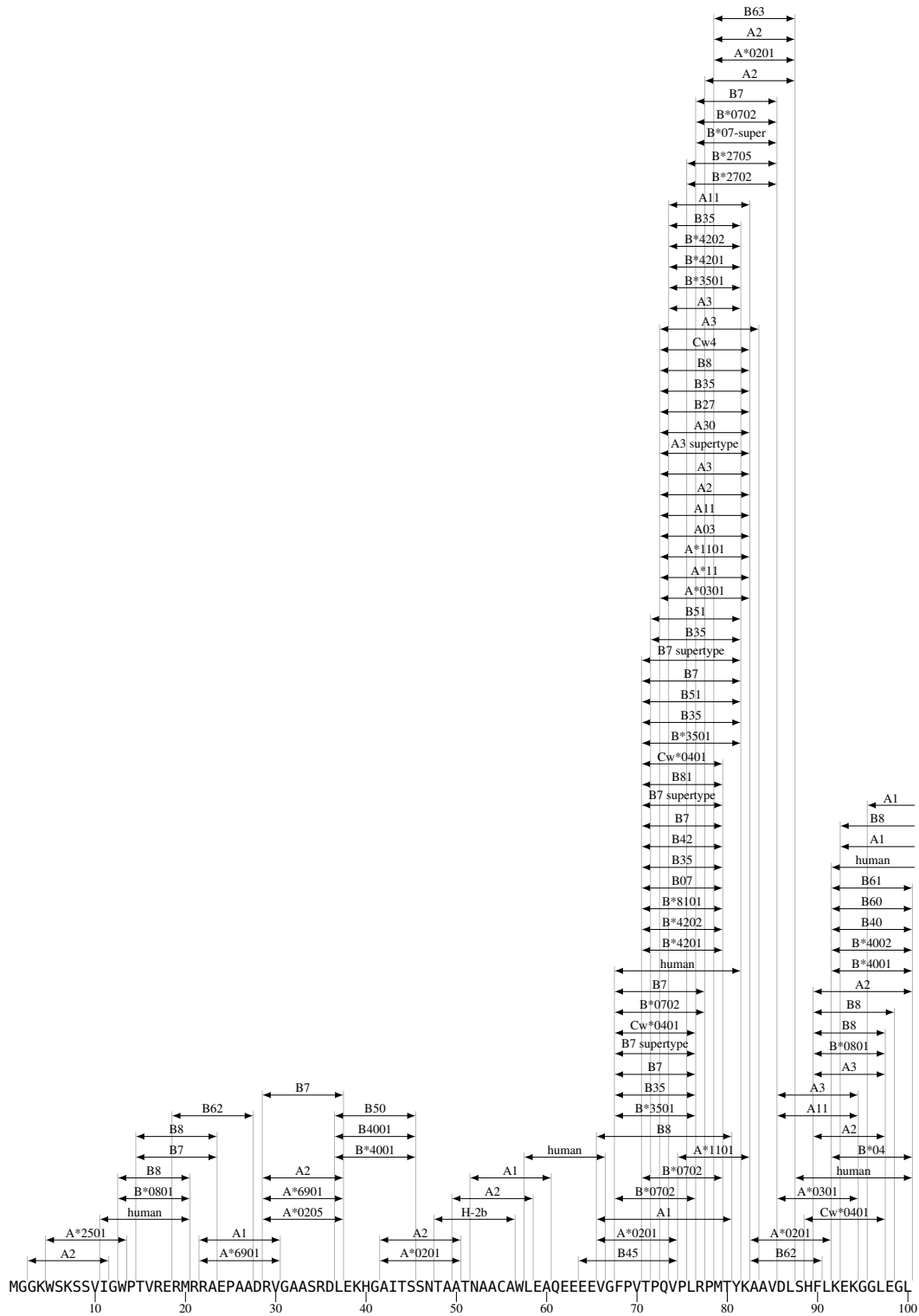


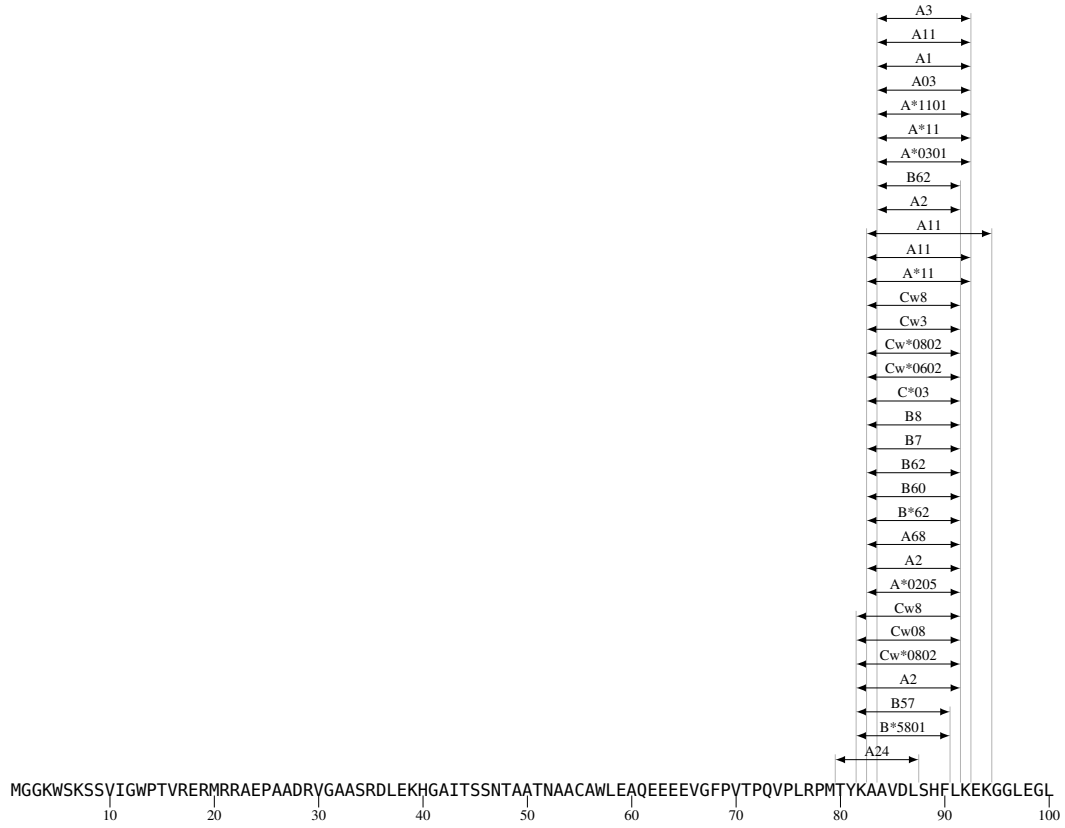


CTL CD8+

II-C-14 Nef CTL/CD8+ Epitope Map

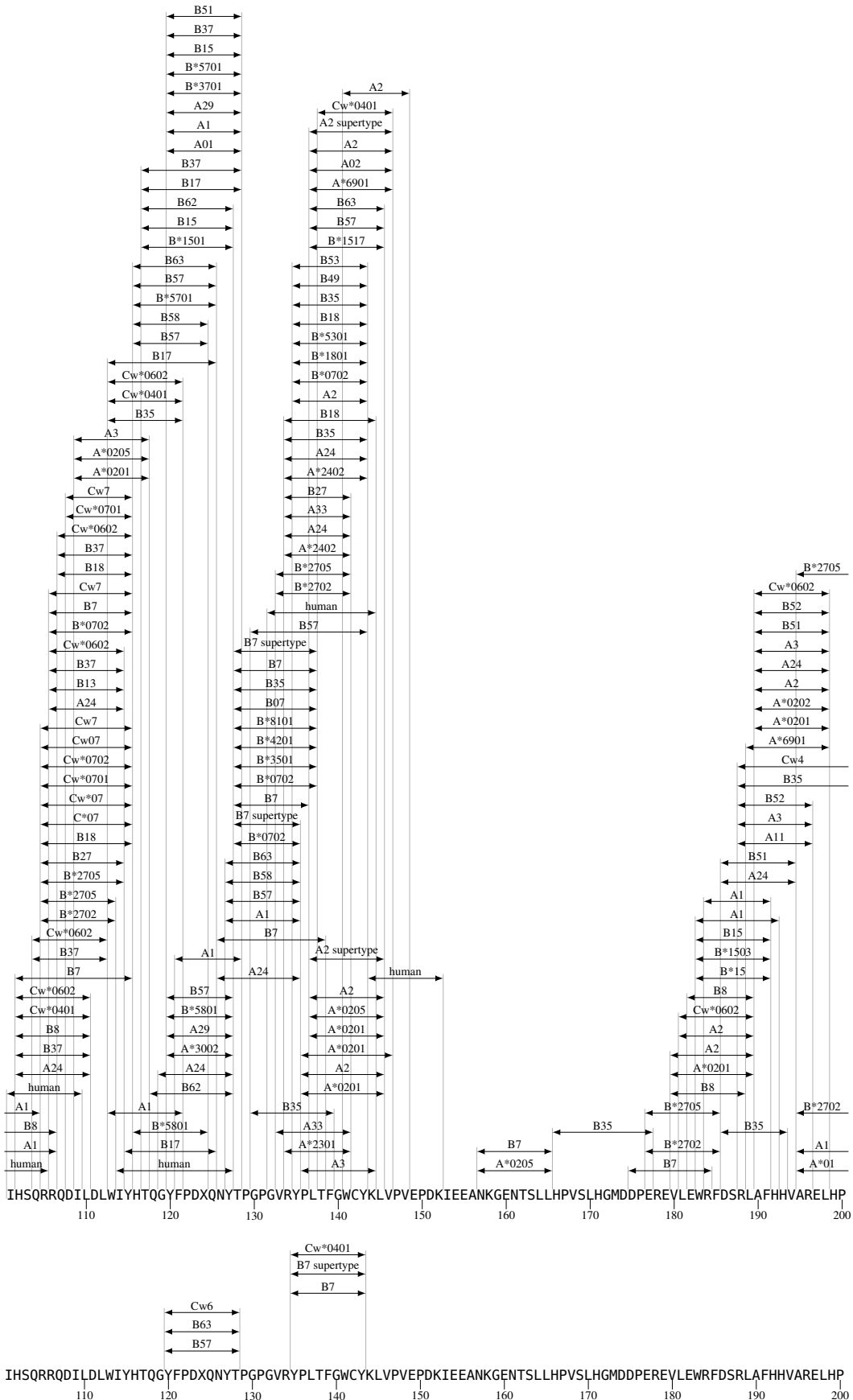
CTL CD8+





CTL CD8+

CTL CD8+



## Nef CTL/CD8+ Epitope Map

## Maps of CTL/CD8+ Epitope Locations Plotted by Protein

B\*2705  
B\*2702  
A1  
A\*01  
Cw4  
B35  
EYFKNC  
206

CTL CD8+

CTL CD8+

**Part III**

# **HIV Helper/CD4+ T-Cell Epitopes**

T-Helper CD4+





## III-A

# Summary

This part includes tables, maps, and associated references of HIV-specific helper T-cell (Th) epitopes from the literature arranged sequentially according to the location of the proteins in the HIV-1 genome. We attempted to make this part as comprehensive as possible, requiring that the epitope be contained within a defined region of a maximum of 30 amino acids, but not that the optimal boundaries be defined. Studies that were based on the analysis of whole proteins are described at the end of each protein section. The same epitope can have multiple entries, as each entry represents a single publication in this part of the database. HLA specificity is usually not determined for Th epitopes. For more recent updates, epitope sequence alignments, and useful search capabilities, please see our web site: <http://www.hiv.lanl.gov/content/immunology>. Helper T-cell responses to proteins with no defined epitopes are listed at the end of each protein section.

Recent studies utilize multiple functions attributed to T cells to define responses, and the simple distinctions of cytotoxic T cells and helper T cells have become blurred as more is learned about the range of responses triggered in CD4 and CD8 positive T cells responding to antigenic stimulus. When adding the most recent studies to the database, we have tried to place T cell responses in a reasonable manner into our traditional helper T cell and CTL parts, and to specify the assay used to measure the response in each study.

### III-A-1 Epitope tables

Each T-helper epitope has a multi-part basic entry:

**HXB2 location:** The viral strain HXB2 (GenBank Accession Number K03455) is used as a reference strain throughout this publication. The position of the defined epitope location relative to the sequence of the HXB2 protein is indicated. The numbering in this table corresponds to the protein maps. Because of HIV-1 variation the epitope may not actually be present in HXB2; rather, the position in HXB2 indicates the position aligned to the epitope. HXB2 was selected as the reference strain because so many studies use HXB2, and because crystal structures for HXB2-related proteins are often available. The precise positions of an epitope on the HXB2 reference strain can be readily obtained using the interactive position locator at our

web site: <http://www.hiv.lanl.gov/content/sequence/LOCATE/locate.html>.

**Author location:** The amino acid positions of the epitope boundaries and the reference sequence are listed as given in the primary publication. Frequently, these positions as published are imprecise, and do not truly correspond to the numbering of the sequence, but they provide a reasonable guide to the peptide's approximate location in the protein. Also, in many cases the reference sequence identification was not provided, and in such cases it is not possible to use these numbers to specify precise locations.

**Epitope:** The amino acid sequence of the epitope of interest as defined in the reference, based on the reference strain used in the study defining the epitope. On occasions when only the position numbers and not the actual peptide sequence were specified in the original publication, we tried to fill in the peptide sequence based on the position numbers and reference strain. If the sequences were numbered inaccurately by the primary authors, or if we made a mistake in this process, we may have misrepresented the binding site's amino acid sequence. Because of this uncertainty, epitopes that were not explicitly written in the primary publication, that we determined by looking up the reference strain and the numbered location, are followed by a question mark in the table.

**Epitope name:** If the epitope has a name attributed by the publication, it is recorded here, e.g. "SL9".

**Subtype:** The subtype under study, if specified in the primary publication; this is generally not specified for B subtype.

**Immunogen:** The antigenic stimulus of the Th response. Often this is an HIV-1 infection. If a vaccine was used as the original antigenic stimulation, not a natural infection, this is noted separately, and additional information about the vaccine antigen is provided as available.

**Species (MHC):** The species responding and MHC or HLA specificity of the epitope.

**Donor MHC:** The HLA genotype of the individual that responded to the epitope.

**Country:** The country where the samples were obtained; this is generally not specified if the study was conducted in the United States.

**Assay type:** Assay used to characterize the response.

**Keywords:** Keywords are a searchable field for the web interface that is included in the T-cell sections of the

printed version to help identify entries of particular interest.

**Reference:** The primary reference (sometimes two or more directly related studies are included). Details for some of the earlier references are in Part V.

Following the entry for a given Th epitope brief comments explain the context in which the epitope was studied and what was learned about the epitope in a given study.

### III-A-2 HIV protein epitope maps

All HIV Th epitopes mapped to within a region of 18 amino acids or less are indicated on the HIV protein epitope maps. The location and HLA restriction elements of Th epitopes are indicated on protein sequences of HXB2. These maps are meant to provide the relative location of defined epitopes on a given protein, but the HXB2 sequence may not actually carry the epitope of interest, as it may vary relative to the sequence for which the epitope was defined. Epitopes with identical boundaries and HLA fields are included in the maps only once. If one laboratory determines HLA presenting molecules at the serotype level (example: A2) and another at the genotype level (example: A\*0201) both will be included in the map. MHC specificities are indicative of the host species; when no MHC presenting molecule is defined, the host species is noted.

### III-A-3 Alignments

To conserve space, no epitope alignments are provided in this book, but they can be generated using the Th epitope search tool at <http://www.hiv.lanl.gov/content/immunology>. The master alignment files from which the epitope alignments were created are available at our web site at <http://www.hiv.lanl.gov/content/sequence/NEWALIGN/align.html>.

## III-B

# HIV Helper/CD4+ T-Cell Epitope Tables

All HIV Helper/CD4+ T-Cell epitopes are arranged by protein position. The table entries are sorted in a nested way—first by protein, then by HXB2 start location within the protein, and finally by HLA presenting molecule. Epitopes for which the HXB2 location is unknown appear at the end of the listing of the protein in which they are located.

### III-B-1 Gag p17 Helper/CD4+ T-cell epitopes

**HXB2 Location** p17 (1–18)  
**Author Location** p17 (1–18 B consensus)  
**Epitope** MGARASVLSGGELDRWEK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This epitope was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** p17 (5–16)  
**Author Location** Gag (5–15)  
**Epitope** ASILRGGKLDKW  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p17 (7–17)  
**Author Location** Gag (7–17)  
**Epitope** VLSGGELDRWE  
**Epitope name** Gag 1.2  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade  
*HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu  
**Species (MHC)** macaque  
**Assay type** T-cell Elispot, Intracellular cytokine staining  
**Keywords** subtype comparisons, memory cells  
**References** Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. VLSGGELDRWE was not reported for human infections.
- The response elicited to the B clade epitope VLSGGELDRWE does not cross-react with the CRF02\_AG form VLtGGELDsWE. The forms VLSGG[e/k]LD[r/ak]WE are prevalent among M group clades.

**HXB2 Location** p17 (9–26)  
**Author Location** p17 (9–26 B consensus)  
**Epitope** SGGELDRWEKIRLRPGGK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 22% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** p17 (10–24)

**Author Location** p17 (242–256)

**Epitope** GGKLDWEKIRLRPG

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag

**Species (MHC)** human

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** vaccine antigen design

**References** Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

**HXB2 Location** p17 (13–23)

**Author Location** Gag (13–23)

**Epitope** LDRWEKIRLRP

**Epitope name** Gag 1.3

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu

**Species (MHC)** macaque

**Assay type** T-cell Elispot, Intracellular cytokine staining

**Keywords** subtype comparisons, memory cells

**References** Amara *et al.* 2005

• Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.

• 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.

• LDRWEKIRLRP was not reported for human infections.

• The response elicited to the B clade epitope LDRWEKIRLRP does not cross-react with the CRF02\_AG form LDsWEKIRLRP. Other clades most commonly carry an A in this position, and C clade consensus carries K (LD[r/ak]WEKIRLRP).

**HXB2 Location** p17 (17–31)

**Author Location** Gag (17–31 HXB-2)

**Epitope** EKIRLRPGGKKKYKL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Koeppel *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

**HXB2 Location** p17 (17–34)

**Author Location** p17 (17–34 B consensus)

**Epitope** EKIRLRPGGKKKYKIKHI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.

- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** p17 (17–34)  
**Author Location** p17 (17–34)  
**Epitope** EKIRLRPGGKKKYKLHKI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Netherlands  
**Assay type** Cytokine production  
**References** Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. EKIRLRPGGKKKYKLHKI had fixation of 1 mutation (EKIRLRPGGKK[k/r]YKLHKI) in 1 of the patients.

**HXB2 Location** p17 (18–42)  
**Author Location** p17 (18–42 PV22)  
**Epitope** KIRLRPGGKKKYKLKHIVWASRELE  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*13)  
**Donor MHC** A29, A30, B35, B8, DRB1\*03, DRB1\*13  
**Keywords** HAART, ART, Th1, Th2  
**References** Lotti *et al.* 2002

- 10/49 chronically HIV-1 infected patients had low p55-Gag-specific CD4+ T cell responses prior to therapy, and these responses remained unchanged 3 and 6 months after initiation of HAART. There was no difference in level of response in those with or without a detectable p55 response.
- For one individual, patient F45 CDC stage A2, CD4+ p55 responding clones were generated. Her response was consistently strong and heterogeneous in terms of HLA restriction and V $\beta$  usage, and some clones had a Th1 cytokine secretion profile (high IFN $\gamma$  production) while some had a Th2 profile (high IL-4 and IL-5 production). 5/10 CD4+ clones could also induce cytotoxicity.
- 4/10 clones from patient F45 had their epitopes mapped using overlapping peptides. Clone 6 recognized this peptide sequence restricted by DRB1\*13. This clone had a high SI (27.1 to p55, 90.6 to peptide) secreted IFN $\gamma$ , indicative of a Th1 response, as well as TNF $\alpha$ . Clone 6 was highly cytotoxic, through a perforin-mediated pathway.

**HXB2 Location** p17 (20–30)  
**Author Location** Gag (25–35)  
**Epitope** RLRPGGKKHYM  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was detectable.

**HXB2 Location** p17 (21–35)  
**Author Location** p17 (21–35 SF2)  
**Epitope** LRPGGKKKYKLKHIV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR13.02)  
**Keywords** escape  
**References** Harcourt *et al.* 1998

- 43 asymptomatic HIV+ individuals were screened for proliferative responses to HIV – 12 showed a response, and dominant epitopes were mapped for two individuals, one in p24 and one in p17.
- Patient 024's naturally occurring variant LRPGGKKKYQLKHIV also elicited a strong proliferative response.
- Naturally occurring variants of this epitope were found within the individual who made this response – several did not stimulate the CD4+ T-cell line that recognized the index peptide, suggestive of immune escape.

**HXB2 Location** p17 (22–29)  
**Author Location** p17 (22–29 LAI)  
**Epitope** RPPGKKKY?  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.
- Schrier lists this peptide as p24(22-29), but it appears to be in p17.

**HXB2 Location** p17 (28–38)  
**Author Location** Gag (32–43)  
**Epitope** HYMLKHLVWAS  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p17 (29–43)  
**Author Location** Gag (29–43 HXB-2)  
**Epitope** YKLVKHIWASRELER  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Koeppel *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

**HXB2 Location** p17 (32–46)  
**Author Location** p17 (32–46 B Consensus)  
**Epitope** KHIVWASRELERFAV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** p17 (33–47)  
**Author Location** p17 (33–47 IIIB, B10)

**Epitope** HIVWASRELERFAVN?

**Immunogen** HIV-1 infection  
**Species (MHC)** human

- References** Wahren *et al.* 1989b; Wahren *et al.* 1989a
- Peptides were identified that commonly evoke T-cell responses – 57% of 90 HIV+ people had a T-cell response to this peptide.

**HXB2 Location** p17 (33–47)  
**Author Location** Gag (33–47 HXB-2)  
**Epitope** HIVWASRELERFAVN  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Koeppel *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

**HXB2 Location** p17 (35–59)  
**Author Location** p17 (35–49 PV22)  
**Epitope** VWASRELERFAVNPGLLETSEGCRQ  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*13)  
**Donor MHC** A29, A30, B35, B8, DRB1\*03, DRB1\*13  
**Keywords** HAART, ART, Th1, Th2, TCR usage  
**References** Lotti *et al.* 2002

- 10/49 chronically HIV-1 infected patients had low p55-Gag-specific CD4+ T cell responses prior to therapy, and these responses remained unchanged 3 and 6 months after initiation of HAART. There was no difference in level of response in those with or without a detectable p55 response.
- For one individual, patient F45 CDC stage A2, CD4+ p55 responding clones were generated. Her response was consistently strong and heterogeneous in terms of HLA restriction and V $\beta$  usage, and some clones had a Th1 cytokine secretion profile (high IFN $\gamma$  production) while some had a Th2 profile (high IL-4 and IL-5 production). 5/10 CD4+ clones could also induce cytotoxicity.
- 4/10 clones from patient F45 had their epitopes mapped using overlapping peptides. Clone 25 recognized this peptide sequence restricted by DRB1\*13 using TCR V $\beta$  5.1. This clone had a SI of 4.9 to p55, 13.7 to peptide, secreted low levels of IFN $\gamma$ , indicative of a Th1 response. Clone 25 had cytotoxic activity, mediated through both a perforin and a Fas-based pathway.

**HXB2 Location** p17 (37–51)  
**Author Location** p17 (37–51 B consensus)  
**Epitope** ASRELERFAVNPGLL  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1302, DRB1\*1501)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This peptide was recognized by 36% of the study group.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 6/8 common HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** p17 (38–53)  
**Author Location** p17 (270–284)  
**Epitope** SRELERFALNPSLLEE  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag  
**Species (MHC)** human  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** vaccine antigen design  
**References** Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 4/8 subjects responded to this epitope.

**HXB2 Location** p17 (39–47)  
**Author Location** p17 (B consensus)  
**Epitope** RELERFAVN  
**Subtype** B  
**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*1302)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), immunodominance  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This epitope was in the overlap between 2 highly reactive peptides; it was fine mapped and found to be presented by DRB\*1302.

**HXB2 Location** p17 (41–51)  
**Author Location** p17 (41–51 B consensus)  
**Epitope** LERFAVNPGLL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*1302)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This core epitope, LERFAVNPGLL, was found to bind to 1/8 HLA-DR proteins tested, DRB\*1302.

**HXB2 Location** p17 (41–55)  
**Author Location** Gag (41–55 HXB-2)  
**Epitope** LERFAVNPGLLETSE  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Koeppel *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

**HXB2 Location** p17 (42–51)  
**Author Location** p17 (B consensus)  
**Epitope** ERFAVNPGLL  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB3\*0202, DRB3\*0301)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), immunodominance  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This epitope was in the overlap between 2 highly reactive peptides, and was fine mapped; 2 different presenting alleles for 2 different clones were determined, and found to be DRB3\*0202, DRB3\*0301.

**HXB2 Location** p17 (42–56)  
**Author Location** p17 (274–289)  
**Epitope** ERFALNPSLLETAEG  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag  
**Species (MHC)** human  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** vaccine antigen design  
**References** Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 4/8 subjects responded to this epitope.

**HXB2 Location** p17 (42–58)  
**Author Location** p17 (42–58 B consensus)  
**Epitope** ERFAVNPGLLETSEGCR  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101, DRB1\*0405, DRB1\*1101, DRB1\*1302)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** supervised treatment interruptions (STI), immunodominance  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 28% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 4/8 tested HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.

**HXB2 Location** p17 (48–58)  
**Author Location** Gag (53–63)  
**Epitope** PGLLETSEGCK  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p17 (70–86)  
**Author Location** p17 (70–86 B Consensus)  
**Epitope** TGSEELRSLNTVALY  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding



**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.

**HXB2 Location** p17 (71–85)

**Author Location** p17 (302–316)

**Epitope** TSEELKSLFVTVATL

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag

**Species (MHC)** human

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** vaccine antigen design

**References** Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

**HXB2 Location** p17 (73–83)

**Author Location** Gag (73–83)

**Epitope** EELRSLYNTVA

**Epitope name** Gag 4.3

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu

**Species (MHC)** macaque

**Assay type** T-cell Elispot, Intracellular cytokine staining

**Keywords** subtype comparisons, memory cells

**References** Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- EELRSLYNTVA was not reported for human infections.
- The response elicited to the B clade epitope EELRSLYNTVA does not cross-react with the CRF02\_AG form EEFK-SLYNIVA. The epitope is however conserved across clades A,B,C,D,F.

**HXB2 Location** p17 (73–89)

**Author Location** p17 (73–89 clade B consensus)

**Epitope** EELRSLYNTVATLYCVH

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1302, DRB1\*1501)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is EELRSLYNTVATLYCVH, shorter LRSLYNTVATLYC is the predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** p17 (75–89)

**Author Location** p17 (306–320)

**Epitope** LKSLFNTVATLYCVH

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag

**Species (MHC)** human

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** vaccine antigen design

**References** Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.

- 2/8 subjects responded to this epitope.

**HXB2 Location** p17 (77–91)  
**Author Location** Gag (77–91 HXB-2)  
**Epitope** SLNTVATLYCVHQ  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No inpatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

**HXB2 Location** p17 (77–94)  
**Author Location** p17 (77–94 B consensus)  
**Epitope** SLYNTVATLYCVHQRIEV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1302, DRB5\*0101)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This peptide was recognized by 25% of the study group.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 6/8 common HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** p17 (77–94)  
**Author Location** p17 (77–94)  
**Epitope** SLYNTVATLYCVHQRIEV  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Netherlands  
**Assay type** Cytokine production  
**References** Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. SLYNTVATLYCVHQRIEV had fixation of 1 mutation (SLYNT[v/i]ATLYCVHQRIEV) in 1 of the patients.

**HXB2 Location** p17 (82–92)  
**Author Location** Gag (87–97)  
**Epitope** VATLYCVHAGI  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was detectable.

**HXB2 Location** p17 (93–107)  
**Author Location** p17 (93–107 IIIB, B10)  
**Epitope** EIKDTKEALDKIEE  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** p17 (118–132)  
**Author Location** p17 (118–132 IIIB, B10)  
**Epitope** AAADTGHSSQVSQNY  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

### III-B-2 Gag p17-p24 Helper/CD4+ T-cell epitopes

**HXB2 Location** p17-p24 (131–18)  
**Author Location** Gag (131–150 LAI)  
**Epitope** NYPIVQNIQGQMVHQAI SPR  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other  
**Species (MHC)** transgenic mouse (DR1)  
**Country** France  
**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** computational epitope prediction, Th1  
**References** Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPSILDIRQGP.

**HXB2 Location** p17-p24 (131–18)  
**Author Location** Gag (131–150 HXB2)  
**Epitope** NYPIVQNIQGQMVHQAI SPR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** DRB1\*1302, DRB1\*1503; DRB1\*0701, DRB1\*1601  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 20-mer peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

### III-B-3 Gag p24 Helper/CD4+ T-cell epitopes

**HXB2 Location** p24 (1–9)  
**Author Location** p24 (133–141 HXB2)  
**Epitope** PIVQNIQGQ  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101)  
**Donor MHC** DQ1, DQ5, DR51, DRB1\*0101, DRB1\*1501  
**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining  
**Keywords** HAART, ART  
**References** Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells  $\mu$ l was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were also recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.
- The TCR that recognized this epitope used V $\beta$ 5.1.

**HXB2 Location** p24 (1–11)  
**Author Location** p24 (1–11 SF2)  
**Epitope** PIVQNLQGQMV  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR1)  
**Keywords** escape  
**References** Harcourt *et al.* 1998

- 43 asymptomatic HIV+ individuals were screened for proliferative responses to HIV – 12 showed a response, and dominant epitopes were mapped for two individuals, one in p24 and one in p17.
- Out of five truncated versions of peptide PIVQNLQGQMVHQAI SPRTL, only p24(1-11) elicited a proliferative response.
- Nine naturally occurring variants of this epitope were found within the individual who made this response – all bound to HLA-DR1, but three did not stimulate the CD4+ T-cell line that recognized the index peptide, suggestive of immune escape.

**HXB2 Location** p24 (1–15)  
**Author Location** p24 (133–147 III B, B10)  
**Epitope** PIVQNIQGQMVHQAI  
**Immunogen** HIV-1 infection  
**Species (MHC)** human

- References** Wahren *et al.* 1989b; Wahren *et al.* 1989a
- Peptides were identified that commonly evoke T-cell responses – 62% of 90 HIV+ people had a T-cell response to this peptide.

**HXB2 Location** p24 (1–22)  
**Author Location** p24 (133–154 SF2)  
**Epitope** PIVQNIQGQMVHQAI SPRTLNA  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Rosenberg *et al.* 1997

- While anti-HIV CD4 Th responses are characteristically undetectable in chronic infections, strong p24-specific proliferative responses were inversely correlated with low viral load in 10 chronically infected people.
- The dominant proliferative response in one of two long term survivors was to this peptide.

**HXB2 Location** p24 (7–21)

**Author Location** Gag (171–185)

**Epitope** QGQMVHQAI SPRTL N

**Epitope name** Gag 171

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Keywords** subtype comparisons

**References** Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds to nine HLA-DR alleles: DRB1\*0101, DRB1\*1501, DRB1\*0401, DRB1\*0405, DRB1\*1302, DRB1\*0701, DRB1\*0901, DRB5\*0101 and DRB4\*0101 with an IC<sub>50</sub> threshold below 1,000 nM.
- This epitope sequence is conserved in 52% of clade B isolates.
- 7/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

**HXB2 Location** p24 (7–21)

**Author Location** p24 (171–185)

**Epitope** QGQMVHQAI SPRTL N

**Epitope name** Gag1

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Country** United Kingdom

**Assay type** proliferation, intracellular cytokine staining

**Keywords** supertype, rate of progression

**References** Boaz *et al.* 2003

- Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.
- Gag1 was 1 of 3 peptides that had a negative correlation between absolute number of responding cells and viral load.

**HXB2 Location** p24 (7–21)

**Author Location** Gag (171–185)

**Epitope** QGQMVHQAI SPRTL N

**Epitope name** Gag 171

**Immunogen** vaccine

**Vector/Type:** DNA with CMV promoter, peptide **Adjuvant:** Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (I-Ab and HLA-DR)

**Donor MHC** H-2b

**Keywords** vaccine-specific epitope characteristics, immunodominance

**References** Livingston *et al.* 2002

- 4 Th HIV epitopes presented by HLA-DR molecules were identified that also could be presented by murine class II molecule I-Ab, enabling testing of vaccine strategies in H-2b mice.
- Responses to pooled peptides, polyepitope peptides in a linear construct or in a branched MAP construct, and a DNA polyepitope construct with a CMV promoter were compared. A linear arrangement in polyepitope construct created a junctional epitope that could be disrupted with the addition of GPGPG spacers. The linear polyepitope construct with the GPGPG spacer worked well in terms of eliciting responses to all 4 peptides, using either DNA or protein for the vaccination.

**HXB2 Location** p24 (9–26)

**Author Location** p24 (9–26 B Consensus)

**Epitope** QMVHQAI SPRTL NAWVKV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** p24 (11–26)

**Author Location** p24 (143–157)

**Epitope** VHQAI SPRTL NAWVKC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

- Matches 3/3 anchor residues for HLA DR: VHQAISPRT

**HXB2 Location** p24 (11–30)  
**Author Location** Gag (143–152 SF2)  
**Epitope** VHQAISPRTLNAWVKVVEEK  
**Immunogen** vaccine  
*Vector/Type:* *Listeria monocytogenes*  
*Strain:* B clade SF2 *HIV component:* p24 Gag  
**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)  
**Keywords** immunodominance, Th1  
**References** Mata & Paterson 1999

- *Listeria monocytogenes* is an intracellular bacterium that lives in the cytoplasm and generates a cell-mediated immune response.
- *L. monocytogenes* vaccine expressing HIV-1 p24 protein (Lm-Gag) was used to stimulate gag-specific CD4+ T cell proliferative responses in BALB/c(H-2d) and C57BL/6(H-2b) mice.
- 2/3 reactive p24 peptides (out of 22 overlapping peptides that span p24) were recognized by both murine strains; this epitope is immunodominant in C57BL/6 mice and also can stimulate a BALB/c response.
- The proliferative response is due to CD4+ IFN- $\gamma$ -producing cells, a Th1 response.

**HXB2 Location** p24 (11–30)  
**Author Location** p24 (143–162 HXB2)  
**Epitope** VHQAISPRTLNAWVKVVEEK  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* *Listeria monocytogenes*  
*Strain:* B clade HXB2 *HIV component:* Gag  
**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)  
**References** Mata & Paterson 1999

- BALB/c and C57BL/6 mice were immunized with *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag.
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm; secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways.
- The class II Th response was probed using 20mer peptides that overlapped by 10; the peptides VHQAISPRTLNAWVKVVEEK and FRDYVDRFYKTLRAEQASQD were recognized in H-2<sup>b</sup> and H-2<sup>d</sup> mice.

**HXB2 Location** p24 (19–38)  
**Author Location** Gag (151–170 HXB2)  
**Epitope** TLNAWVKVVEEKAFSPEVIP  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** DRB1\*0405, DRB1\*0701; DRB1\*1302, DRB1\*1503; DRB1\*0701, DRB1\*1601  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- 1/3 responding patients had autologous sequence exactly matching this peptide.

**HXB2 Location** p24 (21–36)  
**Author Location** p24 (153–167)  
**Epitope** NAWVKVVEEKAFSPEK  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

**HXB2 Location** p24 (22–36)  
**Author Location** p24 (22–36)  
**Epitope** AWVKVVEEKAFSPEV  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag  
**Species (MHC)** human  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** vaccine antigen design  
**References** Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

**HXB2 Location** p24 (23–40)  
**Author Location** p24 (23–40 B Consensus)  
**Epitope** WVKVVEEKAFSPEVIPMF  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.

- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** p24 (23–40)

**Author Location** p24 (23–40)

**Epitope** WKVVEEKAFSPEVIPMF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Netherlands

**Assay type** Cytokine production

**References** Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. WKVVEEKAFSPEVIPMF had fixation of 2 mutations WKV[v/i]EEKAF[s/n]PEVIPMF in 1 of the patients.

**HXB2 Location** p24 (25–39)

**Author Location**

**Epitope** KVVEEKAFSPEVIPM

**Epitope name** G040

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada

**Assay type** proliferation, Flow cytometric T-cell cytokine assay

**Keywords** memory cells

**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** p24 (28–36)

**Author Location** p24 (160–168 HXB2)

**Epitope** EEKAFSPEV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0101)

**Donor MHC** DQ1, DQ5, DR51, DRB1\*0101, DRB1\*1501

**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining

**Keywords** HAART, ART

**References** Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells  $\mu$ l was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were also recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.
- The TCR that recognized this epitope used V $\beta$ 2.

**HXB2 Location** p24 (28–38)

**Author Location** p24 (HXB2)

**Epitope** EEKAFSPEVIP

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DQ5)

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** epitope processing, vaccine antigen design

**References** SenGupta *et al.* 2004

- Multiple HLA class I-restricted and class II-restricted T-cell epitopes were shown to be processed and presented from an exogenously added HIV-1 gag-p24 peptide complexed to a heat shock protein. T-cell recognition of the complex was shown to be inhibited by brefeldin A indicating an endoplasmic reticulum-dependent pathway.

**HXB2 Location** p24 (28–38)

**Author Location** p24 (161–171 NY-5)

**Epitope** EEKAFSPEVIP

**Epitope name** EP11

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DQ5)

**Donor MHC** DQ3, DQ5, DR11, DR14, Drw52

**Country** United States

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** subtype comparisons, rate of progression, acute/early infection, early treatment, variant cross-recognition or cross-neutralization

**References** Norris *et al.* 2004

- 5 CD4+ T cell epitopes in Gag-p24 were studied, and a minimum epitope length of 6-16 amino acids was found to be required for CD4+ T cell proliferation. Cross-clade recognition was found to be impaired in 17/32 variants tested.
- Patient AC-01, who was infected with HIV-1 in 1997, recognized this epitope and epitope EPRGSDIAGT during acute infection, and 19 months post-initiation of ART therapy started during primary infection.

- The epitope EEKAFSPEVIP is highly conserved in B clade. Common variants from other clades were tested and all had markedly diminished responses, including eeRafspevip, eekaLspevip, and eDKafspevip (all found in clade A); eekGf-spevip, eekGfNpevip (clades A and CRF01\_AE); eekafspeIip (clade C); eekafNpevip (clade D).
- Minimum length peptides for the epitopes studied were not particularly optimal, and peptides longer than the minimum, up to 22 amino acids, were often as potent, in marked contrast to CD8+ T-cell responses.

**HXB2 Location** p24 (29–48)

**Author Location** Gag (161–180 HXB2)

**Epitope** EKAFSPEVIPMFSALSEGAT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DRB1\*0701, DRB1\*1601

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- Responding patient had autologous sequence exactly matching this peptide.

**HXB2 Location** p24 (31–41)

**Author Location** Gag (171–181)

**Epitope** AFSPEVIPMFT

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN $\gamma$  CD4+ response). IL-2 response was detectable.

**HXB2 Location** p24 (31–46)

**Author Location** p24 (163–177)

**Epitope** AFSPEVIPMFSALSEC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (A\*0201)

**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.
- Peptide contains a CTL epitope identified in HIV-positive patients.

- Peptide binds to HLA A\*0201 and causes regulation of class I expression on T2 cells.
- Matches 3/3 anchor residues for HLA DR: VIPMFSALS

**HXB2 Location** p24 (31–47)

**Author Location** p24 (31–47 B Consensus)

**Epitope** AFSPEVIPMFSALSEGA

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** p24 (31–48)

**Author Location** p24 (31–48)

**Epitope** AFSPEVIPMFSALSEGAT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Netherlands

**Assay type** Cytokine production

**References** Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. AFSPEVIPMFSALSEGAT had fixation of 2 mutations (AF[s/n]PEVIPMF[s/t]ALSEGAT) in 1 of the patients.

**HXB2 Location** p24 (31–50)

**Author Location** Gag (164–183)

**Epitope** AFSPEVIPMFSALSEGATPQ

**Epitope name** p24.4

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0401)

**Assay type** Tetramer binding

**Keywords** assay standardization/improvement

**References** Scriba *et al.* 2005a

- Conditions required for optimal HLA class II tetramer staining of DR1- and DR4-restricted CD4+ T cells were studied. Staining was rapid and efficient and did not require internalization. Ultrasensitive detection of rare CD4+ T cells was performed by combining tetramer staining with magnetic bead enrichment, and level of detection was much higher than by standard flow-cytometric techniques.

**HXB2 Location** p24 (31–52)

**Author Location** p24 (163–184 SF2)

**Epitope** AFSPEVIPMFSALSEGATPQDL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Rosenberg *et al.* 1997

- Low viral load correlated with strong HIV-1-specific proliferative response.
- A proliferative response to this epitope was detected in two long term survivors.

**HXB2 Location** p24 (33–45)

**Author Location** p24 (33–45 clade B consensus)

**Epitope** SPEVIPMFSALSE

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB1\*0101, DRB1\*0301, DRB1\*0401, DRB1\*0405, DRB1\*1101, DRB1\*1501)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is SPEVIPMFSALSE, shorter VIPMFSALSE was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** p24 (34–49)

**Author Location** p24 (HXB2)

**Epitope** PEVIPMFSALSEGATP

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DR1)

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** epitope processing, vaccine antigen design, characterizing CD8+ T cells

**References** SenGupta *et al.* 2004

- Multiple HLA class I-restricted and class II-restricted T-cell epitopes were shown to be processed and presented from an exogenously added HIV-1 gag-p24 peptide complexed to a heat shock protein. T-cell recognition of the complex was shown to be inhibited by brefeldin A indicating an endoplasmic reticulum-dependent pathway.

**HXB2 Location** p24 (34–49)

**Author Location** p24 (168–177 NY-5)

**Epitope** PEVIPMFSALSEGATP

**Epitope name** PP16

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR1)

**Donor MHC** DQ5, DQ7, DR1, DR11, DRw52

**Country** United States

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** rate of progression, acute/early infection, early treatment, variant cross-recognition or cross-neutralization

**References** Norris *et al.* 2004

- 5 CD4-T cell epitopes in Gag-p24 were studied, and a minimum epitope length of 6-16 amino acids was found to be required for CD4+ T-cell proliferation. Cross-clade recognition was studied and found to be impaired in 17/32 variants tested.
- Patient AC-25 was an acute seroconverter at the time of sampling, infected with HIV-1 in 1998, and given ARVs during primary infection. The study subject was resampled 18 months after initiation of therapy.
- Natural variants of the epitope PEVIPMFSALSEGATP diminished the level of the response, including pepivpmf-PalsegStp and pepivpmfsalsegStp, found in CRF01\_AE; peI-ipmfTalsegatp, clade C; pepivpmfsalSegatp, clade B; pepivpmf-Talsegatp, clades A, B and C; and pepivVfalsegatp, clade A.
- Minimum length peptides for the epitopes studies were not particularly optimal, and peptides longer than the minimum, up to 22 amino acids, were often as potent, in marked contrast to CD8+ T-cell responses.

**HXB2 Location** p24 (34–49)

**Author Location** p24

**Epitope** PEVIPMFSALSEGATP

**Epitope name** PP16

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR1)

**Assay type** proliferation, Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** binding affinity, escape, optimal epitope, antagonism

**References** Norris *et al.* 2006

- This study demonstrates a mechanism of antagonism by a peptide shorter than the minimum length epitope for an HIV p24-specific CD4+ T-cell clone.
- Truncation of the peptide from PEVIPMFSALSEGATP (PP16) to PEVIPMFSALSEG (PG13) rendered the peptide unable to elicit proliferation, IFN- $\gamma$  release, or serine esterase release, even though it retained strong binding to MHC.



- Although both the original and truncated peptide-MHC complexes bound TCR clone, PEVIPMFSALSEGATP-DR1 tetramer bound with higher avidity than PEVIPMFSALSEG-DR1 tetramer, suggesting that tighter association of the peptide-MHC complex with the TCR is associated with the extent of T-cell activation.
- G/P substitution in the original full-length peptide (PEVIPMFSALSE[g/p]ATP) led to complete loss of agonist activity, and PEVIPMFSALSEpATP became antagonistic.

**HXB2 Location** p24 (35–44)

**Author Location** p24 (HXB2)

**Epitope** EVIPMFSALS

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DR4)

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** epitope processing, vaccine antigen design, characterizing CD8+ T cells

**References** SenGupta *et al.* 2004

- Multiple HLA classes I-restricted and class II-restricted T-cell epitopes were shown to be processed and presented from an exogenously added HIV-1 gag-p24 peptide complexed to a heat shock protein. T-cell recognition of the complex was shown to be inhibited by brefeldin A indicating an endoplasmic reticulum-dependent pathway.

**HXB2 Location** p24 (35–44)

**Author Location** p24 (168–177 NY-5)

**Epitope** EVIPMFSALS

**Epitope name** ES10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR4)

**Donor MHC** DQ3, DQ6, DR15, DR4, DRw51, DRw53

**Country** United States

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** rate of progression, acute/early infection, early treatment, variant cross-recognition or cross-neutralization

**References** Norris *et al.* 2004

- 5 CD4-T cell epitopes in Gag-p24 were studied, and a minimum epitope length of 6-16 amino acids was found to be required for CD4+ T-cell proliferation. Cross-clade recognition was studied and found to be impaired in 17/32 variants tested.
- Patient 161J, infected with HIV-1 in the mid 1980s, was 1 of the 2 LTNPs examined. 161J was ART naive.
- Natural variants of the epitope EVIPMFSALS gave diminished responses including evipmfTals, common in clades A, B and C; and evipVfsals, clade A; evipmfsalA, a clade B variant; and elipmfTals, clade C. The exception was the CRF01\_AE variant evipmfPals, which was as reactive as the original peptide tested.
- Minimum length peptides for the epitopes studies were not particularly optimal, and peptides longer than the minimum, up to 22 amino acids, were often as potent, in marked contrast to CD8+ T-cell responses.

**HXB2 Location** p24 (35–44)

**Author Location** p24 (167–176 HXB2)

**Epitope** EVIPMFSALS

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0101)

**Donor MHC** DQ1, DQ5, DR51, DRB1\*0101, DRB1\*1501

**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining

**Keywords** HAART, ART

**References** Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells  $\mu$ l was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were also recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.

**HXB2 Location** p24 (38–48)

**Author Location** Gag (178–188)

**Epitope** PMFALSEGAT

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p24 (39–58)

**Author Location** Gag (171–190 HXB2)

**Epitope** MFSALSEGATPQDLNTMLNT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DRB1\*1302, DRB1\*1503

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- Responding patient had autologous sequence exactly matching this peptide.

**HXB2 Location** p24 (41–56)  
**Author Location** p24 (173–187)  
**Epitope** SALSEGATPQDLNTMC  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

**HXB2 Location** p24 (48–62)  
**Author Location** p24 (180–194)  
**Epitope** TPQDLNTMLNTVGGH  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Adams *et al.* 1997

- One of four immunogenic Gag peptides used in study of proliferative response to p24.
- Homology to an SIV epitope recognized by macaque T-cells.
- T-cells from 8 of 19 HIV+ individuals responded to this epitope.
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) gave increased detection of proliferative response.

**HXB2 Location** p24 (49–63)  
**Author Location** Gag (181–195 HXB2)  
**Epitope** PQDLNTMLNTVGGHQ  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** DRB1\*1302, DRB1\*1503  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- Responding patient had autologous sequence exactly matching this peptide.

**HXB2 Location** p24 (49–64)  
**Author Location** p24 (49–64)  
**Epitope** PQDLNMLNIVGGHQA  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag  
**Species (MHC)** human  
**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** vaccine antigen design  
**References** Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

**HXB2 Location** p24 (49–71)  
**Author Location**  
**Epitope** PQDLNMLNIVGGHQAAMQLKD  
**Epitope name** HIV-VAX-1045  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB\*0101)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design  
**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 2/13 US test subjects responded to this 23-mer by CD4 Elispot assay. The core computer-predicted peptide was LNIVGGHQA.

**HXB2 Location** p24 (51–66)  
**Author Location** p24 (183–197)  
**Epitope** DLNNTMLNTYGGHQAAC  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

**HXB2 Location** p24 (51–82)  
**Author Location** Gag (183–214 LAI)  
**Epitope** DLNNTMLNTVGGHQAAMQLKETINEEAAEWDR  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* lipopeptide  
**Species (MHC)** human  
**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 2/10 reacted to this peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual.
- None of the 12 tested had an IgG response to this peptide.

**HXB2 Location** p24 (53–66)  
**Author Location** Gag (49–51)  
**Epitope** NTMLNTVGGHQAAM  
**Subtype** C

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p24 (59–78)  
**Author Location** Gag (191–210 HXB2)  
**Epitope** VGGHQAAQMQLKETINEEAA?  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** DRB1\*1302, DRB1\*1503  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.
- Responding patient had autologous sequence exactly matching this peptide.

**HXB2 Location** p24 (69–88)  
**Author Location** p24 (201–220 IIIB)  
**Epitope** LKETINEEAAEWDVHPVHA  
**Epitope name** P21  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (DR)  
**Donor MHC** DQ2, DQ3, DR4, DR7  
**Keywords** immunodominance, Th1, Th2, TCR usage  
**References** Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
- Clone 85 recognized this peptide using TCR V $\beta$  8 and 18; the two TCR receptors indicates this limiting dilution represents a mixed population. This clone was only activated by peptide, not by processed protein from vaccinia virus Gag-infected B-LCL.

**HXB2 Location** p24 (69–88)  
**Author Location** Gag (201–220 HXB2)  
**Epitope** LKETINEEAAEWDVHPVHA

**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** DRB1\*1302, DRB1\*1503; DRB1\*0405, DRB1\*0701  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

**HXB2 Location** p24 (71–86)  
**Author Location** p24 (203–220)  
**Epitope** ETINEEAAEWDVHPVHA  
**Subtype** B  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

**HXB2 Location** p24 (71–88)  
**Author Location** p24 (203–220 HXB2)  
**Epitope** ETINEEAAEWDVHPVHA  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101)  
**Donor MHC** DQ1, DQ5, DR51, DRB1\*0101, DRB1\*1501  
**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining  
**Keywords** HAART, ART  
**References** Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells/ul was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.
- The Th clone that recognized this epitope utilized TCR V $\beta$ 17.

**HXB2 Location** p24 (71–92)  
**Author Location** p24 (203–224 HXB2)  
**Epitope** ETINEEAAEWDVHPVHAGPIA  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101)  
**Donor MHC** DQ1, DQ5, DR51, DRB1\*0101, DRB1\*1501  
**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining

**Keywords** HAART, ART

**References** Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells/ul was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.

**HXB2 Location** p24 (73–83)

**Author Location** Gag (205–215)

**Epitope** INEEAAEWDRV

**Epitope name** Gag 11.2

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade  
*HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu

**Species (MHC)** macaque

**Assay type** T-cell Elispot, Intracellular cytokine staining

**Keywords** subtype comparisons, memory cells

**References** Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- CD4 T-cell epitope previously reported for human is ETINEEAAEWDRVHPC. HLA restriction: DRB1\*03, DRB1\*0101.
- The response elicited to the B clade epitope INEEAAEWDRV does not cross-react with the CRF02\_AG form INdEAAEWDRV. The epitope is however conserved in CRF01\_AE and CRF02\_AG consensus sequences. Other clades tend to have L in the last position (INEEAAEWDR[v/l]).

**HXB2 Location** p24 (73–83)

**Author Location** Gag (208–218)

**Epitope** INEEAAEWDR

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p24 (73–97)

**Author Location** p24 (205–229 PV22)

**Epitope** INEEAAEWDRVHPVHAGPIAPGQMR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*03)

**Donor MHC** A29, A30, B35, B8, DRB1\*03, DRB1\*13

**Keywords** HAART, ART, Th1, Th2, TCR usage

**References** Lotti *et al.* 2002

- 10/49 chronically HIV-1 infected patients had low p55-Gag-specific CD4+ T cell responses prior to therapy, and these responses remained unchanged 3 and 6 months after initiation of HAART. There was no difference in level of response in those with or without a detectable p55 response.
- For one individual, patient F45 CDC stage A2, CD4+ p55 responding clones were generated. Her response was consistently strong and heterogeneous in terms of HLA restriction and V $\beta$  usage, and some clones had a Th1 cytokine secretion profile (high IFN $\gamma$  production) while some had a Th2 profile (high IL-4 and IL-5 production). 5/10 CD4+ clones could also induce cytotoxicity.
- 4/10 clones from patient F45 had their epitopes mapped using overlapping peptides. Clone 12 recognized this peptide sequence restricted by DRB1\*03 using TCR V $\beta$  22. This clone had a SI of 12.4 to p55, 49.6 to peptide, secreted low levels of IFN $\gamma$ , indicative of a Th1 response. Clone 12 had cytotoxic activity, mediated through both a perforin and a Fas-based pathway.

**HXB2 Location** p24 (76–85)

**Author Location** p24 (208–217)

**Epitope** EAAEWDRVHP

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Adams *et al.* 1997

- One of four immunogenic Gag peptides used in study of the proliferative response to p24.
- T-cells from 11 of 24 HIV+ individuals responded to this epitope.
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) gave increased detection of proliferative response.

**HXB2 Location** p24 (76–90)

**Author Location** p24 (208–222 IIIB, B10)

**Epitope** EAAEWDRVHPVHAGP

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** p24 (79–88)  
**Author Location** p24 (211–220 HXB2)  
**Epitope** EWDRVHPVHA  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101)  
**Donor MHC** DQ1, DQ5, DR51, DRB1\*0101, DRB1\*1501  
**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining  
**Keywords** HAART, ART  
**References** Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells  $\mu$ l was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were also recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects. Two clones recognized this epitope.

**HXB2 Location** p24 (79–98)  
**Author Location** Gag (211–230 LAI)  
**Epitope** EWDRVHPVHAGPIAPGQMRE  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other  
**Species (MHC)** transgenic mouse (DR1)  
**Country** France  
**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** computational epitope prediction, Th1  
**References** Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

**HXB2 Location** p24 (79–98)  
**Author Location** Gag (211–230 HXB2)  
**Epitope** EWDRVHPVHAGPIAPGQMRE  
**Subtype** B  
**Immunogen** HIV-1 infection

**Species (MHC)** human  
**Donor MHC** DRB1\*0405, DRB1\*0701; DRB1\*0301, DRB1\*0401; DRB1\*0901, DRB1\*1202; DRB1\*0701, DRB1\*1601  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

**HXB2 Location** p24 (81–95)  
**Author Location** p24 (215–229 SF2)  
**Epitope** DRVHPVHAGPIAPGQ  
**Immunogen** vaccine  
*Vector/Type:* virus-like particle (VLP)  
*Strain:* B clade SF2 *HIV component:* p24 Gag  
**Species (MHC)** macaque  
**References** Mills *et al.* 1990

- Responses to 3 T-cell and multiple linear B-cell epitopes were found in vaccinated macaques.

**HXB2 Location** p24 (81–102)  
**Author Location** p24 (213–234 SF2)  
**Epitope** DRVHPVHAGPIAPGQMREPRGS  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Rosenberg *et al.* 1997

- While anti-HIV CD4 Th responses are characteristically undetectable in chronic infections, strong p24-specific proliferative responses were inversely correlated with low viral load in 10 chronically infected people.
- The dominant proliferative response in one of two long term survivors was to this peptide.

**HXB2 Location** p24 (81–102)  
**Author Location** p24 (81–102)  
**Epitope** DRVHPVHAGPIAVPGQMREPRGS  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Netherlands  
**Assay type** Cytokine production  
**References** Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. DRVHPVHAGPIAVPGQMREPRGS had fixation of 1 mutation (DRVHPVHAGPI[a/p]VPGQMREPRGS) in 1 of the patients.

**HXB2 Location** p24 (82–92)

**Author Location** Gag (217–227)

**Epitope** RLHPVHAGPIA

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p24 (85–99)

**Author Location**

**Epitope** PVHGPIAPGQMREP

**Epitope name** G055

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada

**Assay type** proliferation, Flow cytometric T-cell cytokine assay

**Keywords** memory cells

**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** p24 (86–94)

**Author Location** p24 (NY5)

**Epitope** VHAGPIAPG

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DQ7)

**Keywords** HAART, ART, supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection, cross-presentation by different HLA, early treatment, TCR usage

**References** Norris *et al.* 2001

- Gag-specific CD4+ helper T-cell clones were derived from 1 LTNP (CTS-01) and 3 individuals given therapy during acute infection, 2 before (AC-01 and AC-36) and 1 after (AC-25) STI. Gag peptide recognition induced proliferation, IFN- $\gamma$  production, and perforin-mediated cytotoxicity in all CD4+ T-cell clones isolated.

- 3/23 p24-derived peptides tested induced proliferative p24-specific Th cell responses in the LTNP CTS-01. The immunodominant response was to the peptide DRVHPVHAGPI-APGQMREPRGS (81-102), and 9/10 CD4+ T-cell clones reacted with it. One was characterized in detail and used a B $\beta$ 4 TCR.

- The minimum peptide recognized by the clones from CTS-01 was VHAGPIAPG and it was restricted by HLA-DQ7.

**HXB2 Location** p24 (86–94)

**Author Location** p24 (219–227 NY-5)

**Epitope** VHAGPIAPG

**Epitope name** VG9

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DQ7)

**Donor MHC** DQ6, DQ7, DR11, DR15, DRw51, DRw52

**Country** United States

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$

**Keywords** acute/early infection, early treatment, variant cross-recognition or cross-neutralization

**References** Norris *et al.* 2004

- 5 CD4-T cell epitopes in Gag-p24 were studied, and a minimum epitope length of 6-16 amino acids was found to be required for CD4+ T-cell proliferation. Cross-clade recognition was studied and found to be impaired in 17/32 variants tested.
- Patient CTS01, who was infected with HIV-1 in 1998, was an LTNP, and recognized this epitope.
- This epitope VHAGPIAPG was the most variable of the 5 epitopes studied. Only the C variant Ihagpiapg did not diminish the response. All other variations had impaired responses: vhagpVapg, found in clades A, B, C, and D; vQagpVapg, clades B, C, D; AQagpFPpg, IhagpVapg, AhagpVapg, and vQagpiP, all found in clade A; AQagpiapg, clade B; and vPagpiapg, clade C.
- Minimum length peptides for the epitopes studies were not particularly optimal, and peptides longer than the minimum, up to 22 amino acids, were often as potent, in marked contrast to CD8+ T-cell responses.

**HXB2 Location** p24 (87–101)

**Author Location** p24 (219–233 BRU)

**Epitope** HAGPIAPGQMREPRG

**Immunogen** in vitro stimulation or selection

**Species (MHC)** mouse (H-2<sup>b</sup>)

**References** Vaslin *et al.* 1994

- Peptide G2: could prime for *in vitro* immunoproliferative responses and for subsequent IgG responses.

**HXB2 Location** p24 (89–108)

**Author Location** Gag (221–240 HXB2)

**Epitope** GPIAPGQMREPRGSIDIAGTT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DRB1\*0301, DRB1\*0401

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

**HXB2 Location** p24 (93–107)

**Author Location**

**Epitope** PGQMREPRGSDIAGT

**Epitope name** G057

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada

**Assay type** proliferation, Flow cytometric T-cell cytokine assay

**Keywords** memory cells

**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** p24 (94–104)

**Author Location** Gag (229–239)

**Epitope** GQMREPRGSDI

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p24 (96–103)

**Author Location** p24 (228–235 LAI)

**Epitope** MREPRGSD

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** p24 (96–110)

**Author Location** p24 (228–242 IIIB, B10)

**Epitope** MREPRGSKIAGTTST

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** p24 (98–107)

**Author Location** p24 (231–240 NY-5)

**Epitope** EPRGSDIAGT

**Epitope name** ET10

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DQ7)

**Donor MHC** DQ3, DQ5, DR11, DR14, Drw52

**Country** United States

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** acute/early infection, early treatment, variant cross-recognition or cross-neutralization

**References** Norris *et al.* 2004

- 5 CD4-T cell epitopes in Gag-p24 were studied, and a minimum epitope length of 6-16 amino acids was found to be required for CD4+ T-cell proliferation. Cross-clade recognition was found to be impaired in 17/32 variants tested.
- Patient AC-01, who was infected with HIV-1 in 1997, recognized this epitope and epitope EPRGSDIAGT during acute infection, and 19 months post-initiation of ART therapy started during primary infection.
- This was the most variable of the 5 epitopes studied. REPRGSDIAGT natural variants were tested and did not usually diminish the response by much (rDprgsdiagt, clades B and C; and rDprgsdiagA and rGprgsdiagt, both clade C), although the CRF01\_AE variant reprgAdiagt abrogated the response.
- Minimum length peptides for the epitopes studies were not particularly optimal, and peptides longer than the minimum, up to 22 amino acids, were often as potent, in marked contrast to CD8+ T cell responses. This peptide was the exception, as REPRGSDIAGTT, which is elongated by 2 amino acids compared to the minimum epitope, elicited a stronger proliferative immune response as well as IFN- $\gamma$  secretion and cytolysis.

**HXB2 Location** p24 (99–118)

**Author Location** p24 (231–250 IIIB)

**Epitope** PRGSDIAGTTSTLQEIQIGWM

**Epitope name** P24

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DR4)

**Donor MHC** DQ2, DQ3, DR4, DR7

**Keywords** immunodominance, Th1, Th2, TCR usage

**References** Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.

- Clone 6 recognized three peptides including this one with a Th1 response using TCR V $\beta$  6 (6s5A1N1). Sequencing TCR V $\beta$  regions of colonies from clone 6 suggested this was a clonal population. Assays using different peptide concentrations suggest that this peptide does not carry the main epitope of this clone.

**HXB2 Location** p24 (99–118)

**Author Location** Gag (231–250 HXB2)

**Epitope** PRGSDIAGTTSTLQEQIGWM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DRB1\*1302, DRB1\*1503; DRB1\*0405, DRB1\*0701; DRB1\*0301, DRB1\*0401

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present *in vivo*.
- 1/3 responding patients had autologous sequence exactly matching this peptide.

**HXB2 Location** p24 (101–115)

**Author Location** p24 (235–249 SF2)

**Epitope** GSDIAGTTSTLQEQI

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP)

*Strain:* B clade SF2 *HIV component:* p24 Gag

**Species (MHC)** macaque

**References** Mills *et al.* 1990

- Responses to 3 T-cell and multiple linear B-cell epitopes were found in vaccinated macaques – epitope response defined by T-cell clone.

**HXB2 Location** p24 (101–115)

**Author Location** Gag (233–247 HXB-2)

**Epitope** GSDIAGTTSTQEQI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No inpatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

**HXB2 Location** p24 (101–116)

**Author Location** p24

**Epitope** GSDIAGTTSTLQEQIC

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human

**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

**HXB2 Location** p24 (106–116)

**Author Location** Gag (241–251)

**Epitope** GTTSTLQEQIA

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p24 (109–123)

**Author Location**

**Epitope** STLQEQIGWMTNPP

**Epitope name** G061

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada

**Assay type** proliferation, Flow cytometric T-cell cytokine assay

**Keywords** memory cells

**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** p24 (109–128)

**Author Location** Gag (241–260 LAI)

**Epitope** STLQEQIGWMTNPPPIPVGE

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other

**Species (MHC)** transgenic mouse (DR1)

**Country** France



- Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay
- Keywords** computational epitope prediction, Th1
- References** Pajot *et al.* 2007
- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
  - Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQANPDCKTILKALGPA, KTLKALGPAATLEEMMTAC) were novel.
  - Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTLKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors *in vitro*.
  - Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQANPDCKTILKALGPA, NKIVRMYSPTSILDIRQPK.
- HXB2 Location** p24 (109–128)  
**Author Location** p24 (241–260 IIIB)  
**Epitope** STLQEQIGWMTNPPIPVGE  
**Epitope name** P25  
**Immunogen** *in vitro* stimulation or selection  
**Species (MHC)** human  
**Donor MHC** DQ2, DQ3, DR4, DR7  
**Keywords** immunodominance, Th1, Th2, TCR usage  
**References** Venturini *et al.* 2002
- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
  - Clone 50 recognized this peptide with a Th0 response (Th0 means that cytokines characteristic of both Th1 and Th2 responses were stimulated), using TCR V $\beta$  17, and was a homogeneous T-cell population. This clone was only activated by peptide, not by processed protein from vaccinia virus Gag-infected B-LCL.
- HXB2 Location** p24 (110–128)  
**Author Location** p24  
**Epitope** TLQEQIGWMTSNPPIPVGD  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* modified vaccinia Ankara (MVA) *Strain:* A clade, multiple epitope immunogen *HIV component:* p17/p24 Gag  
**Species (MHC)** human  
**Country** United Kingdom  
**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** HAART, ART, vaccine-induced epitopes, therapeutic vaccine  
**References** Ondondo *et al.* 2006
- A vaccinia-gag vaccine stimulated broad functional T helper responses in 16 chronically infected HAART patients. Gag-specific CD4+ T cell responses targeted known and new epitopes, several of which were also recognized by HIV-uninfected subjects.
  - TLQEQIGWMTSNPPIPVGD contains three possible HLA-DR4 binding sequences: LQEQIGWMT, IGWMTSNPP and MTSNPPIPV. Peptides that included these sequences and were at least 10 aa in length stimulated responses.
- HXB2 Location** p24 (111–132)  
**Author Location** p24 (243–264 SF2)  
**Epitope** LQEQIGWMTNPPIPVGEIYKR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Rosenberg *et al.* 1997
- Low viral load correlated with strong HIV-1-specific proliferative response.
  - A proliferative response to this epitope was detected in two long term survivors.
- HXB2 Location** p24 (113–127)  
**Author Location** Gag (248–262)  
**Epitope** EQIAWMTSNPPVPVG  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005
- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
  - 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.
- HXB2 Location** p24 (117–127)  
**Author Location** Gag (251–261)  
**Epitope** WMTSNPPVPVG  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005
- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
  - 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.
- HXB2 Location** p24 (119–133)

**Author Location** p24 (251–265)

**Epitope** TNNPPIPBGEIYKRW

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*1301)

**Keywords** binding affinity, HAART, ART

**References** Blankson & Siliciano 2001; Malhotra *et al.* 2001

- The DRB1\*13-DQB1\*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1\*13-DQB1\*06 positive people, but only 3/14 (21%) of those who did not have DRB1\*13-DQB1\*06, maintained viral suppression for 18 months.
- PBMC from individuals with the haplotype DRB1\*13-DQB1\*06 displayed increased IFN- $\gamma$  secretion and stronger proliferative responses against p24 80 weeks post treatment.
- DRB1\*13-DQB1\*06 was also found to be enriched among long-term non-progressors (LTNPs) (it was in 9/18 versus, versus 21% of the general population)
- This epitope was mapped with truncated peptides using the Elispot assay.
- Two distinct DRB1\*13 epitopes were defined in the peptide region spanning 251 to 270, and this 20-mer bound with very high affinity to DRB1\*1302 – DRB1\*1301 and DRB1\*1302 would be expected to have very similar binding properties.

**HXB2 Location** p24 (119–133)

**Author Location** p24 (119–133)

**Epitope** TNNPPIPBGEIYKRW

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Netherlands

**Assay type** Cytokine production

**References** Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted T-helper epitopes were analyzed. TNNPPIPBGEIYKRW had fixation of R14K mutation (TNNPPIPBGEIYKkKw) in 1 of the patients.

**HXB2 Location** p24 (119–138)

**Author Location** Gag (251–270 HXB2)

**Epitope** TNNPPIPVGEIYKRWIIILGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DRB1\*0503, DRB1\*1302

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous

sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

- Responding patient had autologous sequence exactly matching this peptide.

**HXB2 Location** p24 (121–136)

**Author Location** p24 (253–267)

**Epitope** NPPIPVGGEIYKRWIIC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

**HXB2 Location** p24 (121–140)

**Author Location** Gag (253–272 SF2)

**Epitope** NPPIPVGGEIYKRWILGLNK

**Immunogen** vaccine

*Vector/Type:* Listeria monocytogenes

*Strain:* B clade SF2 *HIV component:* p24 Gag

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** immunodominance, Th1

**References** Mata & Paterson 1999

- *Listeria monocytogenes* is an intracellular bacterium that lives in the cytoplasm and generates a cell-mediated immune response.
- *L. monocytogenes* vaccine expressing HIV-1 p24 protein (Lm-Gag) was used to stimulate gag specific CD4+ T cell proliferative responses in BALB/c(H-2d) and C57BL/6(H-2b) mice.
- 2/3 reactive p24 peptides (out of 22 overlapping peptides that span p24) were recognized by both murine strains; this epitope is immunodominant in BALB/c mice and did not stimulate a C57BL/6 response.
- The proliferative response is due to CD4+ IFN- $\gamma$ -producing cells, a Th1 response.

**HXB2 Location** p24 (121–140)

**Author Location** p24 (253–272 HXB2)

**Epitope** NPPIPVGGEIYKRWIIILGLNK

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* Listeria monocytogenes

*Strain:* B clade HXB2 *HIV component:* Gag

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** immunodominance

**References** Mata & Paterson 1999

- BALB/c and C57BL/6 mice were immunized with *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag.
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm; secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways.
- The class II Th response was probed using 20mer peptides that overlapped by 10; the peptide NPPIPVGGEIYKRWIIILGLNK gave the immunodominant response for the H-2<sup>d</sup> haplotype, but was not recognized in H-2<sup>b</sup> mice.

**HXB2 Location** p24 (121–140)  
**Author Location** Gag (197–205)  
**Epitope** NPPIPVGEIYKRWII LGLNK  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade  
 HXB2 *HIV component:* Gag  
**Species (MHC)** mouse (H-2d)  
**Country** United States  
**Assay type** proliferation, T-cell Elispot  
**Keywords** vaccine antigen design  
**References** Kwak *et al.* 2004

- A recombinant vaccinia virus with HIV-1 Gag replacing the cytoplasmic domain of the B5R protein was shown to induce better primary CD4 response than recombinant vaccinia virus expressing Gag from the TK-locus; CD8 responses were less specific. When immunized BALB/c mice were challenged with a recombinant *Listeria* that expresses HIV-Gag, lower colony counts of *Listeria* were found in the liver and spleen of mice immunized with virus expressing B5R-Gag fusion protein.

**HXB2 Location** p24 (121–152)  
**Author Location** Gag (183–214 LAI)  
**Epitope** NPPIPVGEIYKRWII LGLNKIVRMYSPSILD  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* lipopeptide  
**Species (MHC)** human  
**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 9/10 reacted to this peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in four vaccinees.
- All of the 12 tested had an IgG response to this peptide.

**HXB2 Location** p24 (125–139)  
**Author Location** Gag (257–271 HXB-2)  
**Epitope** PVGEIYKRWII LGLN  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Koeppel *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No inpatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 2/22 patients responded to this peptide.

**HXB2 Location** p24 (125–139)  
**Author Location**  
**Epitope** PVGEIYKRWII LGLN  
**Epitope name** G065  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Canada  
**Assay type** proliferation, Flow cytometric T-cell cytokine assay  
**Keywords** memory cells  
**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** p24 (126–148)  
**Author Location**  
**Epitope** VGEIYKRWII LGLNKIVRMYSPV  
**Epitope name** HIV-VAX-1044  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB\*0101)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design  
**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 7/13 US test subjects responded to this 23-mer by CD4 Elispot assay. The core computer-predicted peptide was WII LGLNKI.

**HXB2 Location** p24 (127–141)  
**Author Location** Gag (294–308)  
**Epitope** GEIYKRWII LGLNKI  
**Epitope name** Gag 294  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR supermotif)  
**Keywords** subtype comparisons  
**References** Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds ten HLA-DR alleles: DRB1\*0101, DRB1\*1501, DRB1\*0405, DRB1\*1101, DRB1\*1302, DRB1\*0701, DRB1\*0802, DRB1\*0901, DRB5\*0101 and DRB4\*0101 with an IC<sub>50</sub> threshold below 1,000 nM.
- This epitope sequence is conserved in 95% of clade B isolates.

- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

**HXB2 Location** p24 (127–141)

**Author Location** p24 (294–308)

**Epitope** GEIYKRWIIILGLNKI

**Epitope name** Gag2

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Country** United Kingdom

**Assay type** Cytokine production, proliferation

**Keywords** supertype, rate of progression

**References** Boaz *et al.* 2003

- Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNP (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNP showed increased numbers of IFN  $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.

**HXB2 Location** p24 (128–137)

**Author Location** p24 (260–269)

**Epitope** EIIYKRWIIILG

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*1301, DRB1\*1302)

**Keywords** binding affinity, HAART, ART, Th1

**References** Blankson & Siliciano 2001; Malhotra *et al.* 2001

- The DRB1\*13-DQB1\*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1\*13-DQB1\*06 positive people, but only 3/14 (21%) of those who did not have DRB1\*13-DQB1\*06, maintained viral suppression for 18 months.
- PBMC from individuals with the haplotype DRB1\*13-DQB1\*06 displayed increased IFN- $\gamma$  secretion and stronger proliferative responses against p24 80 weeks post treatment.
- DRB1\*13-DQB1\*06 was also found to be enriched among long-term non-progressors (it was in 9/18 versus, versus 21% of the general population)
- The truncated peptide that gave the optimal proliferative response for a Th1 phenotype clone was this nine-mer.
- This region, shared by 2 overlapping peptides, was the reactive region for clones from two DRB1\*13 patients, one carried DRB1\*1301 and one DRB1\*1302.
- Two distinct epitopes were defined in the peptide region spanning 251 to 270, and this 20-mer bound with very high affinity to DRB1\*1302 – DRB1\*1301 and DRB1\*1302 would be expected to have very similar binding properties.

**HXB2 Location** p24 (129–143)

**Author Location** Gag (261–275 HXB-2)

**Epitope** IYKRWIIILGLNKIVR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Koeppel *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 2/22 patients responded to this peptide.

**HXB2 Location** p24 (129–148)

**Author Location** p24 (261–280 IIB)

**Epitope** IYKRWIIILGLNKIVRMYSPT

**Epitope name** P27

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human

**Donor MHC** DQ2, DQ3, DR4, DR7

**Keywords** immunodominance, Th1, Th2, TCR usage

**References** Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
- Clone 74 recognized two peptides including this one with a Th1 response using TCR V $\beta$  13 (13s1); it required 200 ng/ml (100 nM) and 1  $\mu$ g/ml (0.5  $\mu$ M) for stimulation by peptides 480-500 and 261-280, respectively. Sequencing TCR V $\beta$  regions of colonies from clone 74 suggested this was a clonal population.

**HXB2 Location** p24 (129–148)

**Author Location** Gag (261–280 HXB2)

**Epitope** IYKRWIIILGLNKIVRMYSPT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DRB1\*0503, DRB1\*1302

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present *in vivo*.
- Responding patient had autologous sequence exactly matching this peptide.

- HXB2 Location** p24 (131–145)  
**Author Location** Gag (298–312)  
**Epitope** KRWIILGLNKIVRMY  
**Epitope name** Gag 298  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR supermotif)  
**Keywords** subtype comparisons  
**References** Wilson *et al.* 2001
- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
  - This epitope binds thirteen HLA-DR alleles: DRB4\*0101, DRB5\*0101, DRB1\*0901, DRB1\*0802, DRB1\*0701, DRB1\*1302, DRB1\*1201, DRB1\*1101, DRB1\*0405, DRB1\*0401, DRB\*0301, DRB1\*1501 and DRB1\*0101, with an IC<sub>50</sub> threshold below 1,000 nM.
  - This epitope sequence is conserved in 94% of clade B isolate.
  - 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)
- HXB2 Location** p24 (131–145)  
**Author Location** p24 (298–312)  
**Epitope** KRWIILGLNKIVRMY  
**Epitope name** Gag3  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR supermotif)  
**Country** United Kingdom  
**Assay type** proliferation, Intracellular cytokine staining  
**Keywords** supertype, rate of progression  
**References** Boaz *et al.* 2003
- Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNP (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naïve.
  - Gag-specific CD4+ T cells in LTNP showed increased numbers of IFN  $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.
- HXB2 Location** p24 (131–145)  
**Author Location** Gag (263–277 LAI)  
**Epitope** KRWIILGLNKIVRMY  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other  
**Species (MHC)** transgenic mouse (DR1)  
**Country** France  
**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay  
**Keywords** computational epitope prediction, Th1

- References** Pajot *et al.* 2007
- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
  - Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
  - Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
  - Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

- HXB2 Location** p24 (131–145)  
**Author Location** p24 (265–279 SF2)  
**Epitope** KRWIILGLNKIVRMY  
**Immunogen** vaccine  
*Vector/Type:* virus-like particle (VLP)  
*Strain:* B clade SF2 *HIV component:* p24 Gag  
**Species (MHC)** macaque  
**References** Mills *et al.* 1990
- Responses to 3 T-cell and multiple linear B-cell epitopes were found in vaccinated macaques – epitope response defined by T-cell clone.

- HXB2 Location** p24 (131–150)  
**Author Location** Gag (264–283)  
**Epitope** KRWIILGLNKIVRMYSPTSI  
**Epitope name** p24.14  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101)  
**Assay type** Tetramer binding  
**Keywords** assay standardization/improvement  
**References** Scriba *et al.* 2005a
- Conditions required for optimal HLA class II tetramer staining of DR1- and DR4-restricted CD4+ T cells were studied. Staining was rapid and efficient and did not require internalization. Ultrasensitive detection of rare CD4+ T cells was performed by combining tetramer staining with magnetic bead enrichment, and level of detection was much higher than by standard flow-cytometric techniques.

- HXB2 Location** p24 (131–150)  
**Author Location** Gag (264–283)  
**Epitope** KRWIILGLNKIVRMYSPTSI  
**Epitope name** p24.14  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101)  
**Assay type** Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** assay standardization/improvement, supervised treatment interruptions (STI)  
**References** Scriba *et al.* 2005b

- HIV-specific T helper cell numbers were studied in patients with early-stage HIV infection, who were given a short course of ART, while on ART, during and after ART cessation.
- Magnetic bead enrichment technique was used to enhance sensitivity of HLA class II tetramer staining. CD4+ T cells were consistently detected at frequencies below the detection limit of direct flow cytometric analysis.
- No significant destruction of CD4+ T cell clones was found when HIV viremia rebounded.

**HXB2 Location** p24 (131–150)

**Author Location** p24 (131–150 clade B consensus)

**Epitope** KRWIILGLNKIVRMYSPTSI

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB, DRB1\*0101, DRB1\*0301, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1302)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is KRWIILGLNKIVRMYSPTSI, shorter WIILGLNKIVRMYSPTSI peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** p24 (131–152)

**Author Location** p24 (263–284 SF2)

**Epitope** KRWIILGLNKIVRMYSPTSI

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Rosenberg *et al.* 1997

- Low viral load correlated with strong HIV-1-specific proliferative response.
- A proliferative response to this epitope was detected in two long term survivors.

**HXB2 Location** p24 (133–143)

**Author Location** Gag (265–275)

**Epitope** WIILGLNKIVR

**Epitope name** Gag 14.2

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade  
*HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu

**Species (MHC)** macaque

**Assay type** T-cell Elispot, Intracellular cytokine staining

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization, memory cells

**References** Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- The similar reported human epitope in this case is KRWIILGLNKIVRMYSPTSI, which is presented by 13 HLA-DR alleles.
- The response elicited to the B clade epitope WIILGLNKIVR cross-reacts with the CRF02\_AG form WIvLGLNKIVR. WIILGLNKIVR is mostly conserved across other clades.

**HXB2 Location** p24 (133–144)

**Author Location** p24 (133–144 B Consensus)

**Epitope** WIILGLNKIVRM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0101, DRB1\*1101, DRB1\*1302, DRB1\*1501, DRB5\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was very often recognized, with responses by 25% of the study group. The core epitope, WIILGLNKIVRM, could bind 5/8 HLA-DR molecules tested.

**HXB2 Location** p24 (133–147)

**Author Location** Gag (265–279 HXB-2)

**Epitope** WIILGLNKIVRMYSPT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DQB1\*0602, DQB1\*0604, DRB1\*1302, DRB1\*1501, DRB3\*0301, DRB5\*0101; DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Koeppel *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 2/22 patients responded to this peptide.

**HXB2 Location** p24 (133–147)

**Author Location**

**Epitope** WIILGLNKIVRMYS

**Epitope name** G067

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada

**Assay type** proliferation, Flow cytometric T-cell cytokine assay

**Keywords** memory cells

**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** p24 (133–150)

**Author Location** p24 (133–150 B Consensus)

**Epitope** WIILGLNKIVRMYSPTSI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1302, DRB1\*1501, DRB5\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 25% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.

- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed very high cross-reactive binding capacity, and bound to 8/8 common HLA-DR molecules.

**HXB2 Location** p24 (135–145)

**Author Location** p24 (135–145 B Consensus)

**Epitope** ILGLNKIVRM

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0401, DRB1\*1302, DRB1\*1501)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was very often recognized, with responses by 25% of the study group. The core epitope, ILGLNKIVRM, could bind 3/8 HLA-DR molecules tested.

**HXB2 Location** p24 (135–154)

**Author Location** p24 (267–286)

**Epitope** ILGLNKIVRMYSPTSILDIR

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Adams *et al.* 1997

- One of four immunogenic Gag peptides used in study of the proliferative response to p24.
- 8 of 24 HIV+ individuals responded to this epitope.
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) gave increased detection of proliferative response.

**HXB2 Location** p24 (135–157)

**Author Location**

**Epitope** ILGLNKIVRMYSPPVSIILDIRQGP

**Epitope name** HIV-VAX-1043

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 3/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was VRMYSFVSI.

**HXB2 Location** p24 (137–151)

**Author Location** Gag (269–285 HXB-2)

**Epitope** GLNKIVRMYSPTSIL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Koeppel *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

**HXB2 Location** p24 (138–152)

**Author Location** p24 (138–152)

**Epitope** LNKIVRMYSFVSILD

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag

**Species (MHC)** human

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** vaccine antigen design

**References** Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 2/8 subjects responded to this epitope.

**HXB2 Location** p24 (139–148)

**Author Location** p24 (271–280 HZ321)

**Epitope** NKIVRMYSPT

**Subtype** AG

**Immunogen** vaccine

*Vector/Type:* gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA), CpG immunostimulatory sequence (ISS)

**Species (MHC)** macaque

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** vaccine-induced epitopes, adjuvant comparison, vaccine antigen design

**References** Silvera *et al.* 2004

- Macaques were immunized with gp120-depleted HIV-1 together with incomplete Freund's adjuvant and CpG-ODN. All four immunized animals had high anti-p24 antibody titers, while three animals showed HIV-1-specific CD4+ and CD8+ T-cell responses. This is one of two CD4+ T-cell epitopes in Gag that was mapped.

**HXB2 Location** p24 (139–157)

**Author Location** p24 (271–290 IIIB)

**Epitope** NKIVRMYSPTSILDIRQGP

**Epitope name** P28

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (DR4)

**Donor MHC** DQ2, DQ3, DR4, DR7

**Keywords** immunodominance, Th1, Th2, TCR usage

**References** Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
- Clone 6 recognized three peptides including this one with a Th1 response using TCR V $\beta$  6 (6s5A1N1). Sequencing TCR V $\beta$  regions of colonies from clone 6 suggested this was a clonal population. Assays using different peptide concentrations suggest that this peptide, 271-290, contains the main epitope of this clone. Upon activation, clone 6 was observed to induce a cytopathic effect in the adherent layer of fibroblasts expressing HLA DR4W14 and -W15. Clone 6 was activated in response to vaccinia virus Gag-infected B-LCL, so it could recognize naturally processed epitopes.
- Clone 37 recognized this peptide sequence with a Th2 response using TCR V $\beta$  3, and was a homogeneous T-cell population. This clone was only activated by peptide, not by processed protein from vaccinia virus Gag-infected B-LCL.
- Clone 97 recognized this peptide sequence with a using TCR V $\beta$  9 and 14; the two TCR receptors used indicates this limiting dilution represents a mixed population. This clone was only activated by peptide, not by processed protein from vaccinia virus Gag-infected B-LCL.

**HXB2 Location** p24 (139–158)

**Author Location** Gag (271–290 LAI)

**Epitope** NKIVRMYSPTSILDIRQGP

**Subtype** B

**Immunogen** vaccine



*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other

**Species (MHC)** transgenic mouse (DR1)

**Country** France

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** computational epitope prediction, Th1

**References** Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQANPDCKTILKALGPA, KTLKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTLKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

**HXB2 Location** p24 (139–158)

**Author Location** Gag (271–290 HXB2)

**Epitope** NKIVRMYSPTSILDIRQGPK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DRB1\*0701, DRB1\*1601

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

**HXB2 Location** p24 (140–148)

**Author Location** p24 (272–280 HXB2)

**Epitope** KIVRMYSPT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0101)

**Donor MHC** DQ1, DQ5, DR51, DRB1\*0101, DRB1\*1501

**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining

**Keywords** HAART, ART

**References** Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells/ul was determined. Eleven clonotypes were found

among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.

- The Th clone that recognized this epitope utilized TCR V $\beta$  5.2.

**HXB2 Location** p24 (140–149)

**Author Location** Gag (272–281)

**Epitope** KIVRMYSPTS

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DR4)

**Assay type** proliferation

**Keywords** variant cross-recognition or cross-neutralization

**References** Venturini *et al.* 2006

- Cross-reactivity of a human HIV-1 gag-specific CD4+ T cell clone obtained from an HIV-1 seronegative donor was studied using combinatorial peptide library analysis. Peptides from other pathogens were able to activate T cell clone.
- HIV gag peptides with several mutations in KIVRMYSPTS, corresponding to the existing HIV strains were able to strongly activate the T cell clone.
- 2 bacterial peptides from Burkholderia cepacia (KLARLYTPAR) and from Ralstonia pickettii (TLARLYTPVR) activated the T cell clone with the same potency as the HIV peptides.

**HXB2 Location** p24 (141–156)

**Author Location** p24 (273–287)

**Epitope** IVRMYSPTSILDIRQC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.
- Matches 3/3 anchor residues for HLA DR: IVRMYSPTS

**HXB2 Location** p24 (141–158)

**Author Location** p24 (141–158 B Consensus)

**Epitope** IVRMYSPTSILDIRQGPK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 17% of the study group.

- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP responses corresponded to many peptides, comparable to acute STI.

**HXB2 Location** p24 (141–158)

**Author Location** p24 (141–158)

**Epitope** IVRMYSPTSILDIRQGPK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Netherlands

**Assay type** Cytokine production

**References** Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. IVRMYSPTSILDIRQGPK had fixation of 1 mutation (IVRMYSPT[t/v]SILDIRQGPK) in 1 of the patients.

**HXB2 Location** p24 (146–160)

**Author Location** p24 (278–292 IIIB, B10)

**Epitope** SPTSILDIRQGPK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** p24 (149–168)

**Author Location** p24 (281–300 IIIB)

**Epitope** SILDIRQGPKPFRDYVDRF

**Epitope name** P29

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DR4)

**Donor MHC** DQ2, DQ3, DR4, DR7

**Keywords** immunodominance, Th1, Th2, TCR usage

**References** Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.

- Clone 6 recognized three peptides including this one with a Th1 response using TCR V $\beta$  6 (6s5A1N1). Sequencing TCR V $\beta$  regions of colonies from clone 6 suggested this was a clonal population. Assays using different peptide concentrations suggest that this peptide does not carry the main epitope of this clone.

**HXB2 Location** p24 (150–169)

**Author Location** p24 (282–301)

**Epitope** ILDIRQGPKPFRDYVDRFY

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** p24 (151–166)

**Author Location** p24 (283–297)

**Epitope** LDIRQGPKPFRDYVC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.

**HXB2 Location** p24 (153–167)

**Author Location**

**Epitope** IRQGPKPFRDYVDR

**Epitope name** G072

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada

**Assay type** proliferation, Flow cytometric T-cell cytokine assay

**Keywords** memory cells

**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** p24 (155–177)

**Author Location** p24 (287–309)

**Epitope** QGPKPFRDYVDRFYKTLRAEQA

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse

**References** Nakamura *et al.* 1997

- Mice immunized with this peptide generated proliferative responses, CTLs and antibodies.
- This immunogenic domain is from a highly conserved region of p24.

**HXB2 Location** p24 (156–170)

**Author Location** p24 (288–302 IIIB, B10)

**Epitope** GPKEPFRDYVDRFYK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** p24 (156–173)

**Author Location** p24 (156–173 B Consensus)

**Epitope** GPKEPFRDYVDRFYKTLR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** p24 (156–174)

**Author Location** p24 (287–306)

**Epitope** QPKEPFRDYVDRFYKTLRA

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Adams *et al.* 1997

- One of four immunogenic Gag peptides used in study of the proliferative response to p24.
- T-cells from 5 of 21 HIV+ individuals responded to this epitope.
- Improved assay system (increase in culture time to 8 days and addition of IL-2 to cultures) gave increased detection of proliferative response.

**HXB2 Location** p24 (157–165)

**Author Location** p24 (289–297 HXB2)

**Epitope** PKEPFRDYV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DQ5)

**Donor MHC** DQ1, DQ5, DR51, DRB1\*0101, DRB1\*1501

**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining

**Keywords** HAART, ART

**References** Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells  $\mu$ l was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.

**HXB2 Location** p24 (159–178)

**Author Location** Gag (291–310 LAI)

**Epitope** EPFRDYVDRFYKTLRAEQAS

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other

**Species (MHC)** transgenic mouse (DR1)

**Country** France

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** computational epitope prediction, Th1

**References** Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQANPDCKTILKALGPA, KTLKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTLKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

**HXB2 Location** p24 (159–178)

**Author Location** Gag (291–310 HXB2)

**Epitope** EPFRDYVDRFYKTLRAEQAS

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DRB1\*1302, DRB1\*1503; DRB1\*0405, DRB1\*0701; DRB1\*0701, DRB1\*1601

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

**HXB2 Location** p24 (159–178)  
**Author Location** Gag (291–310 HXB2)  
**Epitope** EPFRDYVDRFYKTLRAEQAS  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** DRB1\*1302, DRB1\*1503; DRB1\*0405, DRB1\*0701; DRB1\*0701, DRB1\*1601; DRB1\*0301, DRB1\*0401  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**References** Boritz *et al.* 2007

- CD4+ targeted P24 HXB2 peptides were compared with autologous sequences in 9 chronic untreated patients. 10 of 26 peptides in 5 responding patients exactly matched autologous sequences, indicating that CD4+ T cell responses can persist in chronic HIV-1 infection despite recognition of epitopes present in vivo.

**HXB2 Location** p24 (161–171)  
**Author Location** Gag (296–306)  
**Epitope** FRDYVDRFFKT  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p24 (161–180)  
**Author Location** Gag (294–313)  
**Epitope** FRDYVDRFYKTLRAEQASQD  
**Epitope name** p24.17  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101)  
**Assay type** Tetramer binding  
**Keywords** assay standardization/improvement  
**References** Scriba *et al.* 2005a

- Conditions required for optimal HLA class II tetramer staining of DR1- and DR4-restricted CD4+ T cells were studied. Staining was rapid and efficient and did not require internalization. Ultrasensitive detection of rare CD4+ T cells was performed by combining tetramer staining with magnetic bead

enrichment, and level of detection was much higher than by standard flow-cytometric techniques.

**HXB2 Location** p24 (161–180)  
**Author Location** Gag (294–313)  
**Epitope** FRDYVDRFYKTLRAEQASQD  
**Epitope name** p24.17  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101)  
**Assay type** Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** assay standardization/improvement, supervised treatment interruptions (STI)  
**References** Scriba *et al.* 2005b

- HIV-specific T helper cell numbers were studied in patients with early-stage HIV infection, who were given a short course of ART, while on ART, during and after ART cessation.
- Magnetic bead enrichment technique was used to enhance sensitivity of HLA class II tetramer staining. CD4+ T cells were consistently detected at frequencies below the detection limit of direct flow cytometric analysis.
- No significant destruction of CD4+ T cell clones was found when HIV viremia rebounded.

**HXB2 Location** p24 (161–180)  
**Author Location** Gag (293–312 SF2)  
**Epitope** FRDYVDRFYKTLRAEQASQD  
**Immunogen** vaccine  
**Vector/Type:** *Listeria monocytogenes*  
**Strain:** B clade SF2 *HIV component:* p24 Gag  
**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)  
**Keywords** Th1  
**References** Mata & Paterson 1999

- *Listeria monocytogenes* is an intracellular bacterium that lives in the cytoplasm and generates a cell-mediated immune response.
- *L. monocytogenes* vaccine expressing HIV-1 p24 protein (Lm-Gag) was used to stimulate gag specific CD4+ T cell proliferative responses in BALB/c(H-2d) and C57BL/6(H-2b) mice.
- 2/3 reactive p24 peptides (out of 22 overlapping peptides that span p24) were recognized by both murine strains; this peptide stimulated a response in both BALB/c and C57BL/6 mice.
- The proliferative response is due to CD4+ IFN- $\gamma$ -producing cells, a Th1 response.

**HXB2 Location** p24 (161–180)  
**Author Location** p24 (293–312 HXB2)  
**Epitope** FRDYVDRFYKTLRAEQASQD  
**Subtype** B  
**Immunogen** vaccine  
**Vector/Type:** *Listeria monocytogenes*  
**Strain:** B clade HXB2 *HIV component:* Gag  
**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)  
**References** Mata & Paterson 1999

- BALB/c and C57BL/6 mice were immunized with *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag.

- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm; secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways.
- The class II Th response was probed using 20mer peptides that overlapped by 10; the peptides VHQAISPRTLNAWVKVVEEK and FRDYVDRFYKTLRAEQASQD were recognized in H-2<sup>b</sup> and H-2<sup>d</sup> mice.

**HXB2 Location** p24 (163–175)

**Author Location** Gag (295–307)

**Epitope** DYVDRFYKTLRAE

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR0101)

**Assay type** Cytokine production, proliferation, Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Iyasere *et al.* 2003

- Fifteen patients receiving HAART with strong CD4+ proliferative responses to HIV antigens while on therapy were examined, to see the effects of viremia on these responses during treatment interruptions. Increased viremia occurred in 12/15 patients during at least one treatment interruption. Anti-HIV proliferative responses were inhibited during viremia, but IFN $\gamma$  production to Gag, Pol, and Nef peptide pools were maintained.
- IL-2 production diminished during viremia, and exogenous IL-2 revived *in vitro* proliferation of HIV-specific T-cells to Gag or Pol DR0101 epitopes in a tetramer, as well as Gag-specific total CD4 T-cell responses.

**HXB2 Location** p24 (163–177)

**Author Location** p24 (295–309)

**Epitope** DYVDRFYKTLRAEQA

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*1302)

**Keywords** HAART, ART

**References** Blankson & Siliciano 2001; Malhotra *et al.* 2001

- The DRB1\*13-DQB1\*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1\*13-DQB1\*06 positive people, but only 3/14 (21%) of those who did not have DRB1\*13-DQB1\*06, maintained viral suppression for 18 months.
- PBMC from individuals with the haplotype DRB1\*13-DQB1\*06 displayed increased IFN- $\gamma$  secretion and stronger proliferative responses against p24 80 weeks post treatment.
- DRB1\*13-DQB1\*06 was also found to be enriched among long-term non-progressors (it was in 9/18 versus, versus 21% of the general population)
- This epitope was mapped with truncated peptides using the Elispot assay, and is highly conserved.

**HXB2 Location** p24 (163–177)

**Author Location** p24 (295–309)

**Epitope** DYVDRFYKTLRAEQA

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*1302)

**Keywords** HAART, ART

**References** Blankson & Siliciano 2001; Malhotra *et al.* 2001

- The DRB1\*13-DQB1\*06 haplotype is associated with maintained viral suppression after HAART – 7/7 early-treated DRB1\*13-DQB1\*06 positive people, but only 3/14 (21%) of those who did not have DRB1\*13-DQB1\*06, maintained viral suppression for 18 months.
- PBMC from individuals with the haplotype DRB1\*13-DQB1\*06 displayed increased IFN- $\gamma$  secretion and stronger proliferative responses against p24 80 weeks post treatment.
- DRB1\*13-DQB1\*06 was also found to be enriched among long-term non-progressors (it was in 9/18 versus, versus 21% of the general population)
- This epitope was mapped with truncated peptides using the Elispot assay, and is highly conserved.

**HXB2 Location** p24 (164–181)

**Author Location** p24 (164–181 B Consensus)

**Epitope** YVDRFYKTLRAEQASQEV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1302, DRB1\*1501, DRB5\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed very high cross-reactive binding capacity, and bound to 8/8 tested common HLA-DR molecules.
- This peptide was the most often recognized, with a responses by 58% of the study group.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.

**HXB2 Location** p24 (164–181)

**Author Location** p24 (164–181)

**Epitope** YVDRFYKTLRAEQASQEV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Netherlands

**Assay type** Cytokine production

**References** Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. YVDRFYKTLRAEQASQEV had fixation of 1 mutation (YVDRFYKTLRAEQA[s/t]QEV) in 1 of the patients.

**HXB2 Location** p24 (165–179)

**Author Location** Gag (297–311 HXB-2)

**Epitope** VDRFYKTLRAEQASQ

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DQB1\*0602, DQB1\*0604, DRB1\*1302, DRB1\*1501, DRB3\*0301, DRB5\*0101; DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102; DQB1\*0301, DRB1\*0401, DRB1\*1101, DRB3\*0202, DRB4\*0103; DQB1\*0202, DQB1\*0602, DRB1\*0701, DRB1\*1501, DRB4\*0103, DRB5\*0101

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No inpatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 4/22 patients responded to this peptide.

**HXB2 Location** p24 (166–178)

**Author Location** p24

**Epitope** DRFFKTLRAEQAT

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* modified vaccinia Ankara (MVA) *Strain:* A clade, multiple epitope immunogen *HIV component:* p17/p24 Gag

**Species (MHC)** human

**Country** United Kingdom

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** HAART, ART, vaccine-induced epitopes, therapeutic vaccine

**References** Ondondo *et al.* 2006

- A vaccinia-gag vaccine stimulated broad functional T helper responses in 16 chronically infected HAART patients. Gag-specific CD4+ T cell responses targeted known and new epitopes, several of which were also recognized by HIV-uninfected subjects.

- Both DRFFKTLRAEQAT and FFKTLRAEQATQE stimulated stronger response than 15-mer originally tested peptide DRFFKTLRAEQATQE. Peptides lacking FFKTLRAEQA (FKTLRAEQATQEVKNW and RDYVDRFFKTLRAEQA) did not stimulate a response, suggesting that the FFKTLRAEQA, which fits the predicted peptide-binding motif for HLA-DRB1\*1301 and \*1302, represented the core binding region of two distinct epitopes in this region.

**HXB2 Location** p24 (166–180)

**Author Location** p24 (166–180)

**Epitope** DRFFKTLRAEQATQE

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* A clade consensus *HIV component:* Gag

**Species (MHC)** human

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** vaccine antigen design

**References** Goonetilleke *et al.* 2006

- Healthy volunteers were immunized with a vaccine containing clade A consensus gag plus a string of immunodominant CD8+ epitopes from the gag, pol, nef and env genes. 12/16 vaccinees produced T-cell responses mainly mediated by CD4+ T cells. Of the responders, 11/12 developed responses to previously-identified CD4+ epitopes, and 5/12 also developed CD8+ T-cell responses to the epitope string.
- 3/8 subjects responded to this epitope.

**HXB2 Location** p24 (167–178)

**Author Location** p24 (167–178 B Consensus)

**Epitope** RFYKTLRAEQAS

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1501, DRB5\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was the most often recognized, with responses by 58% of the study group. The core epitope, RFYKTLRAEQAS, could bind 7/8 HLA-DR molecules tested.

**HXB2 Location** p24 (168–179)  
**Author Location** p24 (168–179 B Consensus)  
**Epitope** FYKTLRAEQASQ  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*1101, DRB5\*0101)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was the most often recognized, with responses by 58% of the study group. The core epitope, FYKTLRAEQASQ, could bind 4/8 HLA-DR molecules tested.

**HXB2 Location** p24 (168–180)  
**Author Location** p24 (168–180 B Consensus)  
**Epitope** FYKTLRAEQASQE  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*1101, DRB1\*1501, DRB5\*0101)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was the most often recognized, with responses by 58% of the study group. The core epitope, FYKTLRAEQASQE, could bind 6/8 HLA-DR molecules tested.

**HXB2 Location** p24 (168–180)  
**Author Location** p24  
**Epitope** FFKTLRAEQATQE

**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* modified vaccinia Ankara (MVA) *Strain:* A clade, multiple epitope immunogen *HIV component:* p17/p24 Gag

**Species (MHC)** human  
**Country** United Kingdom  
**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** HAART, ART, vaccine-induced epitopes, therapeutic vaccine  
**References** Ondondo *et al.* 2006

- A vaccinia-gag vaccine stimulated broad functional T helper responses in 16 chronically infected HAART patients. Gag-specific CD4+ T cell responses targeted known and new epitopes, several of which were also recognized by HIV-uninfected subjects.
- Both DRFFKTLRAEQAT and FFKTLRAEQATQE stimulated stronger response than 15-mer originally tested peptide DRFFKTLRAEQATQE. Peptides lacking FKTLRAEQA (FKTLRAEQATQEVKNW and RDYVDRFFKTLRAEQA) did not stimulate a response, suggesting that the FKTLRAEQA, which fits the predicted peptide-binding motif for HLA-DRB1\*1301 and \*1302, represented the core binding region of two distinct epitopes in this region.

**HXB2 Location** p24 (169–177)  
**Author Location** p24 (169–177 B Consensus)  
**Epitope** YKTLRAEQA  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB1\*0101)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- This is the core of the peptide and was most often recognized, with responses by 58% of the study group. This core epitope could bind only 1/8 of HLA-DR molecules tested.

**HXB2 Location** p24 (169–178)  
**Author Location** p24 (301–310 HZ321)  
**Epitope** YKTLRAEQAS  
**Subtype** AG  
**Immunogen** vaccine

*Vector/Type:* gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* virus *Adjuvant:*

Incomplete Freund's Adjuvant (IFA), CpG immunostimulatory sequence (ISS)

**Species (MHC)** macaque

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** vaccine-induced epitopes, adjuvant comparison, vaccine antigen design

**References** Silvera *et al.* 2004

- Macaques were immunized with gp120-depleted HIV-1 together with incomplete Freund's adjuvant and CpG-ODN. All four immunized animals had high anti-p24 antibody titers, while three animals showed HIV-1-specific CD4+ and CD8+ T-cell responses.

**HXB2 Location** p24 (169–179)

**Author Location** Gag (301–311)

**Epitope** YKTLRAEQASQ

**Epitope name** Gag 15.5

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade *HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu

**Species (MHC)** macaque

**Assay type** T-cell Elispot, Intracellular cytokine staining

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization, memory cells

**References** Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- The similar reported human epitopes in this case is DYV-DRFYKTLRAEQA. HLA restriction: DRB1\*1302.
- The response elicited to the B clade epitope YKTLRAEQASQ cross-reacts with the CRF02\_AG form fKTLRAEQAtQ. Other clades mostly have same substitutions in these positions ([y/f]KTLRAEQA[s/t]Q).

**HXB2 Location** p24 (169–183)

**Author Location**

**Epitope** YKTLRAEQASQEVKN

**Epitope name** G076

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada

**Assay type** proliferation, Flow cytometric T-cell cytokine assay

**Keywords** memory cells

**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.

- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** p24 (169–188)

**Author Location** Gag (301–320 LAI)

**Epitope** YKTLRAEQASQEVKNWMTET

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other

**Species (MHC)** transgenic mouse (DR1)

**Country** France

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** computational epitope prediction, Th1

**References** Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQANPDKCTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQANPDKCTILKALGPA, NKIVRMYSPTSILDIRQGPK.

**HXB2 Location** p24 (173–187)

**Author Location** Gag (301–315 HXB-2)

**Epitope** RAEQASQEVKNWMTET

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** DQB1\*0301, DQB1\*0601, DRB1\*1303, DRB1\*1502, DRB3\*0101, DRB5\*0102

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**References** Koeppel *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

**HXB2 Location** p24 (175–199)

**Author Location** p17 (307–331 PV22)



**Epitope** EQASQEVKNWMTETLLVQANPDCK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*03)

**Donor MHC** A29, A30, B35, B8, DRB1\*03, DRB1\*13

**Keywords** HAART, ART, Th1, Th2, TCR usage

**References** Lotti *et al.* 2002

- 10/49 chronically HIV-1 infected patients had low p55-Gag-specific CD4+ T cell responses prior to therapy, and these responses remained unchanged 3 and 6 months after initiation of HAART. There was no difference in level of response in those with or without a detectable p55 response.
- For one individual, patient F45 CDC stage A2, CD4+ p55 responding clones were generated. Her response was consistently strong and heterogeneous in terms of HLA restriction and V $\beta$  usage, and some clones had a Th1 cytokine secretion profile (high IFN $\gamma$  production) while some had a Th2 profile (high IL-4 and IL-5 production). 5/10 CD4+ clones could also induce cytotoxicity.
- 4/10 clones from patient F45 had their epitopes mapped using overlapping peptides. Clone 26 recognized this peptide sequence restricted by DRB1\*03. This clone had a SI of 4.1 to p55, 5.3 to peptide, secreted high levels of IFN- $\gamma$ , indicative of a Th1 response, but also IL-4 and IL-5. Clone 26 had no cytotoxic activity.

**HXB2 Location** p24 (181–198)

**Author Location** p24 (313–327)

**Epitope** VKNWMTETLLVQANANC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Bedford *et al.* 1997

- Epitope elicits a primary proliferative response in PBMC from uninfected donors.
- Matches 3/3 anchor residues for HLA DR: VKNWMTETL

**HXB2 Location** p24 (185–202)

**Author Location** p24 (185–202 B Consensus)

**Epitope** MTETLLVQANPDCKTIL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.

- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.

**HXB2 Location** p24 (189–203)

**Author Location** Gag (324–338)

**Epitope** LLVQANPDCKTILR

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** India

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** subtype comparisons

**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p24 (189–208)

**Author Location** Gag (321–340 LAI)

**Epitope** LLVQANPDCKTILKALGPA

**Subtype** B

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other

**Species (MHC)** human, transgenic mouse (DR1)

**Country** France

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay

**Keywords** computational epitope prediction, Th1

**References** Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQANPDCKTILKALGPA, KTILKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTILKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors in vitro.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQANPDCKTILKALGPA, NKIVRMYSPTSILDIRQGPK.

**HXB2 Location** p24 (199–217)

**Author Location** Gag (331–350 LAI)

**Epitope** KTILKALGPAATLEEMMTA

**Subtype B****Immunogen** HIV-1 infection, vaccine*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag *Adjuvant:* Other**Species (MHC)** human, transgenic mouse (DR1)**Country** France**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** computational epitope prediction, Th1**References** Pajot *et al.* 2007

- HLA class I/II-transgenic, H-2 class I/II knockout mice, previously used to characterize responses to Hepatitis B vaccine, were used in this study to analyze the HLA-DR1-restricted HIV-1 Gag epitopes.
- Peptides were selected with the TEPITOPE algorithm. Of 9 selected peptides 7 were previously reported epitopes and 2 (LLVQNANPDCKTILKALGPA, KTLKALGPAATLEEMMTAC) were novel.
- Human relevance of the 2 novel epitopes was established by assaying PBMC from HIV-1-infected long term asymptomatic subjects. KTLKALGPAATLEEMMTA primed CD4+ cells from 2 HLA-DR1 seronegative donors *in vitro*.
- Th1 helper potential was demonstrated for 7 structurally conserved epitopes and was particularly strong with YKTLRAEQASQEVKNWMTET, LLVQNANPDCKTILKALGPA, NKIVRMYSPSILDIRQGPK.

**HXB2 Location** p24 (201–215)**Author Location** Gag (333–347 HXB-2)**Epitope** ILKALGPAATLEEMM**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human**Country** United States**Assay type** CD4 T-cell Elispot - IFN $\gamma$ **References** Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

**HXB2 Location** p24 (205–219)**Author Location** Gag (337–351 HXB-2)**Epitope** LGPAATLEEMMTACQ**Subtype B****Immunogen** HIV-1 infection**Species (MHC)** human**Country** United States**Assay type** CD4 T-cell Elispot - IFN $\gamma$ **References** Koeppe *et al.* 2006

- The study measured CD4+ T-cell responses against epitopes in Gag p17 and p24 and concurrent endogenous plasma HIV-1 RNA epitope sequence variation. No intrapatient protein sequence variation was found in identified epitopes, indicating that escape from CD4-positive T-cell responses is not a common process *in vivo*.
- 1/22 patients responded to this peptide.

**HXB2 Location** p24**Author Location** p24**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A01, A32, B\*1410, B15; A\*3101, A68, B\*4403, B51**Country** Spain**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$ **Keywords** HAART, ART, supervised treatment interruptions (STI)**References** Arnedo-Valero *et al.* 2004

- T cell immune responses following STI were monitored in two chronically HIV-1 infected partners (A and B) who had contracted HIV-1 during 1992. STI induced strong transitory CD4+ and CD8+ T cell responses in both patients. The viruses remained very closely related over 10 years, despite the two individuals having different HLA types; the authors suggest the maintained similarity does not support a strong role for HLA driven HIV diversity as has been claimed in Moore *et al.* (Science 2002).
- During the second treatment stop, patient A developed a strong proliferative response to p24, and multiple strong CD8+ T cell responses to Env, Pol, Gag and Nef. This patient was able to control viral load for two years follow up without therapy. Patient B developed a very weak CD4+ T cell response against p24 during breaks in therapy, and had CD8+ responses to two epitopes. Patient A: A01, A32, B\*1410, B15; Patient B: A\*3101, A68, B\*4403, B51.

**HXB2 Location** p24**Author Location** p24**Epitope****Immunogen** vaccine*HIV component:* p24 Gag *Adjuvant:* Keyhole Limpet Haemocyanin (KLH)**Species (MHC)** human**Country** United States**Assay type** proliferation, Th support of CTL response, Delayed-type hypersensitivity (DTH)**Keywords** HAART, ART, immune dysfunction**References** Lange *et al.* 2004

- ART treated HIV-1 infected patients with strong lymphoproliferative responses to HIV p24 did not have enhanced immune responses relative to those that had low level proliferative responses. Immune function was measured by DTH to diphtheria/tetanus-toxoid and Keyhole limpet hemocyanin, maturation and frequency of CD8+ T cells, frequency of CD4 and CD8+ T cells, and cytotoxic molecules on HIV specific T cells.
- A higher level of persistent viral replication in circulating CD4+ cells was associated with patients who showed high lymphoproliferative responses to HIV p24.

**HXB2 Location** p24**Author Location** p24**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Country** United States

**Assay type** proliferation, Intracellular cytokine staining

**Keywords** HAART, ART, immune dysfunction

**References** Palmer *et al.* 2004

- The cytokine and maturation profiles as well as the proliferative capacity of HIV-1 Gag-specific CD4+ T cells was analyzed in 4 groups of HIV-1 infected patients: HAART treated, HAART suppressed, treatment naive and untreated, slowly progressing. Measurements of Gag-specific CD4+ T cell maturation, proliferation and plasma viremia indicate that virologic control is impaired due to HIV-1 effects on the maturation profiles of CD4+ T cells.

**HXB2 Location** p24

**Author Location** p24 (HXB2)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human

**Country** Canada, Kenya

**Assay type** proliferation, Intracellular cytokine staining

**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Alimonti *et al.* 2005

- CD4+ T cell responses were studied in high-risk HIV-seronegative (Kenya) women, HIV-positive women (Kenya) and low-risk HIV-seronegative women (Canada), using 15mer peptides (overlapping by 11 amino acids) spanning p24 HXB2 sequence.
- Compared to HIV-positive women, high-risk HIV-seronegative women had significantly lower level of CD4+ specific immune activation and apoptosis. Lower proportion of HIV-seronegative women showed responses by the short-term CD4+ specific intracellular cytokine staining assay, while the proportions showing responses by the long-term CD8+-depleted T cell proliferation assay were similar. HIV-seronegative responders had 4.5-fold stronger response than the HIV+ group.

### III-B-4 Gag p2p7p1p6 Helper/CD4+ T-cell epitopes

**HXB2 Location** p2p7p1p6 (8–25)

**Author Location** (clade B consensus)

**Epitope** TNSATIMMQRGNFRNQRK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*02, A\*03, B\*1402, B\*5101, Cw\*15, DRB1\*01AH, DRB1\*1302

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.

- QKQEtDKELYPLASLk variant was present at first time point and coincided with a positive CD4+ response. QKQEtDKELYPLASLk variant was present 4 weeks later and response was lost.

**HXB2 Location** p2p7p1p6 (16–30)

**Author Location** (clade B consensus)

**Epitope** QRGNFRNQRKTVKCF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*02, A\*03, B\*1402, B\*5101, Cw\*15, DRB1\*01AH, DRB1\*1302

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- QkGNFRNQgKTVKCF variant was present at first time point and coincided with a positive CD4+ response. QkGNFNK-NQgKTVKCF variant was present 4 weeks later and also coincided with a positive response.

**HXB2 Location** p2p7p1p6 (18–37)

**Author Location** p24 (384–400 HXB2)

**Epitope** GNFRNQRKIVKCFNCGKEGH

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR15/51)

**Donor MHC** DQ1, DQ5, DR51, DRB1\*0101, DRB1\*1501

**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining

**Keywords** HAART, ART

**References** Boritz *et al.* 2003

- HIV infected individuals with advanced disease often have only weak or undetectable HIV specific Th responses, and HAART can sometimes restore Th HIV recognition in such cases. The repertoire of Th responses to p24 in an individual who responded to HAART after having a CD4+ T-cell count of 0 cells/ul was determined. Eleven clonotypes were found among 13 clones, recognizing eight distinct epitopes, with a range of MHC affinities and functional avidities. Multiple Gag p24 peptides were recognized using CD4 Elispot assays based on samples from six additional HAART-treated CD4 T-cell-reconstituted subjects.
- The two Th clones that recognized this epitope utilized TCR V $\beta$ 2 and B $\beta$ 8.1.

**HXB2 Location** p2p7p1p6 (22–32)

**Author Location** Gag (385–395)

**Epitope** NQRKIVKCFNC

**Epitope name** Gag 20.2

**Immunogen** vaccine

*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade  
*HIV component:* Env, Gag, Protease, Rev, RT, Tat, Vpu

**Species (MHC)** macaque**Assay type** T-cell Elispot, Intracellular cytokine staining**Keywords** subtype comparisons, memory cells**References** Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation.
- The similar reported human epitope in this case is GNFRN-QRKIVKCFNCGKEGH. HLA restriction: DR15/51.
- The response elicited to the B clade epitope NQRKIVKCFNC does not cross-react with the CRF02\_AG form gQR-IKCFNC. The epitope is highly variable across other clades.

**HXB2 Location** p2p7p1p6 (27–37)**Author Location** Gag (390–400)**Epitope** VKCFNCGKGEH**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Country** India**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** subtype comparisons**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p2p7p1p6 (30–44)**Author Location** p15 (393–407 IIIIB, B10)**Epitope** FNCGKEGHTARNCR**Immunogen** HIV-1 infection**Species (MHC)** human**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** p2p7p1p6 (37–52)**Author Location** p15 (37–52 B Consensus)**Epitope** HIAKNCRAPRKKGCWK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Country** United States**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.

**HXB2 Location** p2p7p1p6 (43–60)**Author Location** (clade B consensus)**Epitope** RAPRKKGCWKCGKEGHQM**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A\*0201, A\*290201, B\*1501, B\*4403, Cw\*0304, Cw\*1601, DRB1\*0401, DRB1\*0701; A\*0101, A\*0201, B\*4001, C\*0304, DRB1\*0801, DRB1\*1301**Country** United States**Assay type** CD4 T-cell Elispot - IFN $\gamma$ **Keywords** escape**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- In one patient, HIArNcKAPRKKGCWK variant was present at first time point and there was no CD4+ response. HIArNcK-APRrKGCWK variant was present 4 weeks later and coincided with a positive response. In another patient, B consensus variant HIAKNCRAPRKKGCWK was present at first time point and coincided with a positive response. HIAKNCRAsRKKGCWK variant present four weeks later coincided with a significantly diminished response.

**HXB2 Location** p2p7p1p6 (43–60)**Author Location** (clade B consensus)**Epitope** RAPRKKGCWKCGKEGHQM**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A\*0201, A\*290201, B\*1501, B\*4403, Cw\*0304, Cw\*1601, DRB1\*0401, DRB1\*0701**Country** United States**Assay type** CD4 T-cell Elispot - IFN $\gamma$ **Keywords** escape**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.

- In one patient, kAPRKKGCWKCCKEGHQM variant was present at first time point and there was no CD4+ response. kAPRrKGCWKCCKEGHQM variant was present 4 weeks later and coincided with a positive response. In another patient, B consensus variant RAPRKKGCWKCCKEGHQM was present at first time point and coincided with no response. RA<sub>s</sub>RKKGCWKCCKEGHQM variant present four weeks later also coincided with no response.

**HXB2 Location** p2p7p1p6 (55–69)  
**Author Location** p15 (418–432 IIIB, B10)  
**Epitope** KEGHQMKDC<sub>T</sub>ERQAN

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a
- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** p2p7p1p6 (60–74)  
**Author Location** p15 (423–437 IIIB, B10)  
**Epitope** MKDC<sub>T</sub>ERQANFLGKI

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a
- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** p2p7p1p6 (62–72)  
**Author Location** Gag (426–436)  
**Epitope** DC<sub>T</sub>ERQANFLG  
**Subtype** C

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** India  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay  
**Keywords** subtype comparisons  
**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p2p7p1p6 (66–81)  
**Author Location** p15 (66–81 B consensus)  
**Epitope** RQANFLGKIWPSHKGR  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human (DR01\*0401, DRB1\*0101, DRB1\*0405, DRB1\*1101, DRB1\*1302, DRB1\*1501, DRB5\*0101)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

#### References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  Elispot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 28% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell Elispot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 7/8 tested HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.

**HXB2 Location** p2p7p1p6 (72–89)  
**Author Location** p15 (72–89 B Consensus)  
**Epitope** GKIWPSHKGRPGN<sub>T</sub>LQSR  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

#### References Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  Elispot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 17% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell Elispot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.

**HXB2 Location** p2p7p1p6 (76–83)  
**Author Location** p24 (439–446 LAI)  
**Epitope** PSYKGRPG  
**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human

**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.
- Schrier lists this peptide as p24(439-446), but because of the numbering used for Gag epitopes, we placed it in p2p7p1p6.

**HXB2 Location** p2p7p1p6 (83–97)**Author Location** p15 (446–460 BRU)**Epitope** GNFLQSRPEPTAPPA**Immunogen** *in vitro* stimulation or selection**Species (MHC)** mouse (H-2<sup>b</sup>)**References** Vaslin *et al.* 1994

- Peptide G4: could prime for *in vitro* immunoproliferative responses and for subsequent IgG responses.

**HXB2 Location** p2p7p1p6 (89–96)**Author Location** p24 (466–473 LAI)**Epitope** REETTPPS**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.
- Schrier lists this peptide as p24(466-473), but it is in p2p7p1p6.

**HXB2 Location** p2p7p1p6 (93–112)**Author Location** p15 (93–112 B Consensus)**Epitope** TAPPEESFRFGREETTPSQK**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Country** United States**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.

**HXB2 Location** p2p7p1p6 (98–112)**Author Location** p15 (473–487 IIIB, B10)**Epitope** ESFRSGVETTPPQK**Immunogen** HIV-1 infection**Species (MHC)** human**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- Peptides were identified that commonly evoke T-cell responses – 50% of 90 HIV+ people had a T-cell response to this peptide.

**HXB2 Location** p2p7p1p6 (103–120)**Author Location** (clade B consensus)**Epitope** GEETTPSQKQEPIDKEL**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A\*2402, A\*680301, B\*3502, B\*3905, Cw\*0401, Cw\*0702, DRB1\*0407, DRB1\*1104**Country** United States**Assay type** CD4 T-cell Elispot - IFN $\gamma$ **Keywords** escape**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- GEEITTPSQKQEtIDKEL variant was present at first time point and coincided with a positive CD4+ response. GEEITTPSQKQEtIDKEL variant was present 4 weeks later and response was lost.

**HXB2 Location** p2p7p1p6 (104–113)**Author Location** Gag (466–476)**Epitope** FEETTPAPPKQ**Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Country** India**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** subtype comparisons**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was detectable.

**HXB2 Location** p2p7p1p6 (106–116)**Author Location** Gag (469–479)**Epitope** TTTTPPQKQEPI**Epitope name** Gag 24.3**Immunogen** vaccine**Vector/Type:** DNA prime with modified vaccinia Ankara (MVA) boost **Strain:** B clade **HIV component:** Env, Gag, Protease, Rev, RT, Tat, Vpu**Species (MHC)** macaque**Assay type** T-cell Elispot, Intracellular cytokine staining**Keywords** subtype comparisons, memory cells**References** Amara *et al.* 2005

- Clade B DNA/MVA HIV vaccine was shown to raise a broad cross-reactive cellular immune response for peptides based on the CRF02\_AG consensus Gag in macaques. The activity was better-conserved for CD8 than CD4 T cells.
- 3/5 CD8 epitopes and 2/8 CD4 epitopes were conserved across multiple HIV-1 clades. All 5 CD8, and 4/8 of the CD4 epitopes that were recognized in vaccinated macaques have also been reported for human infections, indicating cross-species conservation. TTTTPQKQEPI was not reported for human infections.
- The response elicited to the B clade epitope TTTTPQKQEPI does not cross-react with the CRF02\_AG form ipssP-KQEPr. The epitope is highly variable across other clades.

**HXB2 Location** p2p7p1p6 (111–127)

**Author Location** p15 (111–127 B Consensus)

**Epitope** QKQEPIDKELYPLASLR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 17% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPers responded to many peptides, comparable to acute STI.

**HXB2 Location** p2p7p1p6 (111–127)

**Author Location** (clade B consensus)

**Epitope** QKQEPIDKELYPLASLR

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*2402, A\*680301, B\*3502, B\*3905, Cw\*0401, Cw\*0702, DRB1\*0407, DRB1\*1104

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- QKQEtIDKELYPLASLk variant was present at first time point and coincided with a positive CD4+ response. QKQEtDKELYPLASLk variant was present 4 weeks later and response was lost.

**HXB2 Location** p2p7p1p6 (117–131)

**Author Location** p6 (32–46 clade B consensus)

**Epitope** DKELYPLASLRSLFG

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1501, DRB5\*0101)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is DKELYPLASLRSLFG, shorter LYPLASLRS was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** p2p7p1p6 (117–137)

**Author Location** Gag p6 (480–500 IIIB)

**Epitope** DKELYPLTSLRSLFGNDPSSQ

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**Donor MHC** DQ2, DQ3, DR4, DR7

**Keywords** immunodominance, Th1, Th2, TCR usage

**References** Venturini *et al.* 2002

- PBMC from a seronegative donor, the healthy brother of a pair of monozygotic twins discordant for HIV-1 infection, were used to generate HIV-1 Gag-specific CD4+ T-cell clones by *in vitro* immunization with HIV-1 overlapping 20mer peptides spanning p55. Six clones were generated by limiting dilution. All reacted with p24 except one which recognized a p24 peptide and a p6 peptide. All CD4+ T cell clones were HLA class II DR restricted.
- Clone 74 recognized two peptides, including this one, with a Th1 response using TCR V $\beta$  13 (13s1); it required 200 ng/ml (100 nM) and 1  $\mu$ g/ml (0.5  $\mu$ M) for stimulation by peptides 480-500 and 261-280, respectively. Sequencing TCR V $\beta$  regions of colonies from clone 74 suggested this was a clonal population. Clone 74 was activated in response to vaccinia virus Gag-infected B-LCL, so it could recognize naturally processed epitopes.

**HXB2 Location** p2p7p1p6 (118–128)

**Author Location** Gag (479–489)

**Epitope** KDREPLTSLKS

**Subtype C****Immunogen** HIV-1 infection**Species (MHC)** human**Country** India**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** subtype comparisons**References** Kaushik *et al.* 2005

- T cell responses to Gag consensus C peptides were studied in C-infected patients from India. CD8+ responses were stronger and broader than CD4+ responses. IFN- $\gamma$  response was higher in both CD8+ and CD4+ T cells than corresponding IL-2 response, that was detectable only in CD4+ T cells.
- 1/25 patients responded to this peptide (IFN- $\gamma$  CD4+ response). IL-2 response was not detectable.

**HXB2 Location** p2p7p1p6 (118–137)**Author Location** p15 (118–137 B Consensus)**Epitope** KELYPLASLRSLFGNDPSSQ**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Country** United States**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 17% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**III-B-5 Gag Helper/CD4+ T-cell epitopes****HXB2 Location** Gag**Author Location** p24 (IIIB)**Epitope****Immunogen** in vitro stimulation or selection**Species (MHC)** human (A\*0201)**Keywords** dendritic cells**References** Engelmayer *et al.* 2001

- Recombinant canarypox virus vector containing HIV-1 sequences, upon infection of mature dendritic cells, can trigger specific lysis *in vitro* by T-cells from HIV-1 infected individuals at levels comparable to the response seen to HIV carried in vaccinia vectors.
- Recombinant canarypox virus vector containing HIV-1 sequences can also stimulate HIV-specific IFN- $\gamma$  CD4+ helper T cell responses to Gag from bulk or purified CD4+ T cells.

**HXB2 Location** Gag**Author Location** p55**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human (DRB1\*03, DRB1\*13)**Donor MHC** A29, A30, B35, B8, DRB1\*03, DRB1\*13**Keywords** HAART, ART, Th1, Th2, TCR usage**References** Lotti *et al.* 2002

- 10/49 chronically HIV-1 infected patients had low p55-Gag-specific CD4+ T cell responses prior to therapy, and these responses remained unchanged 3 and 6 months after initiation of HAART. There was no difference in level of response in those with or without a detectable p55 response.
- For one individual, patient F45 CDC stage A2, CD4+ p55 responding clones were generated. Her response was consistently strong and heterogeneous in terms of HLA restriction and V $\beta$  usage. Two clones were DRB1\*13 restricted and used TCR V $\beta$  17+19 or 5.1. Three clones were DRB1\*03 restricted and used TCR V $\beta$  22. Some clones had a Th1 cytokine secretion profile (high IFN $\gamma$  production) while some had a Th2 profile (high IL-4 and IL-5 production).

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** vaccine*Vector/Type:* DNA *HIV component:* Gag**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Qiu *et al.* 2000

- Mice were injected with plasmid DNA at 0, 2 and 4 weeks and lymphocyte proliferation was measured after 6 weeks with recombinant p24 protein.
- Secreted HIV-1 Gag expression vectors generated a stronger response than standard Gag or cytoplasmic Gag expression vectors.
- IFN- $\gamma$  levels were increased compared to an undetectable IL-4 response.
- CTL levels were also increased in secreted Gag expression vaccination studies.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** vaccine*Vector/Type:* DNA, DNA with protein boost*Strain:* B clade LAI *HIV component:* Gag,Nef, Tat *Adjuvant:* IL-18**Species (MHC)** mouse (H-2<sup>d</sup>)**Keywords** Th1, Th2**References** Billaut-Mulot *et al.* 2001



- DNA vaccinated BALB/c mice primed and boosted with a multiepitopic vaccine with IL18 showed lymphoproliferative responses 7 weeks post immunization.
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime + DNA boost was more effective than DNA prime + protein boost.
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine resulted in Th1 cytokines production (IL-2 and IFN- $\gamma$ ) in spleen cell cultures stimulated by Tat and Gag, while Th2 cytokines IL-4 and IL-10 production was not detectable.
- Co-administration of IL18 increased T-cell responses but decreased anti-HIV antibody levels.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** vaccine*Vector/Type:* coxsackievirus *HIV component:* p24 Gag**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Halim *et al.* 2000

- An avirulent rec coxsackievirus (CB4-P) construct was generated that can express p24 Gag sequences – CB4-P is attenuated even in immunodeficient mice and T help responses can be elicited from peptides embedded in a surface loop of the VP1 capsid.
- This paper describes the vaccine strategy and generation of constructs, and employs amino-terminal fusion of Gag sequences to the viral polyprotein with subsequent cleavage to elicit CTL responses via MHC class I presentation in BALB/c mice.

**HXB2 Location** Gag**Author Location** gp120 (V3) and p24 (IIIB, MN, BH10)**Epitope****Subtype** A, B**Immunogen** vaccine*Vector/Type:* virus-like particle (VLP)  
*Strain:* A clade UG5.94UG018, B clade IIIB  
*HIV component:* Gag, gp120**Species (MHC)** mouse (H-2<sup>d</sup>)**Keywords** subtype comparisons**References** Buonaguro *et al.* 2002

- Different HIV strains were used for different regions: gp120 A clade UG5.94UG018; Gag HIV-1 IIIB
- BALB/c mice were given intraperitoneal immunization in the absence of adjuvants with virus-like particles (VLPs) expressing recombinant subtype A gp120 and Pr55gag.
- High dose-independent humoral responses were elicited against both gp120 and p24 peptides, and CTL responses were observed against target cells carrying vaccinia expressed gp120 and Gag.

**HXB2 Location** Gag**Author Location** Gag (HXB2)**Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* Listeria monocytogenes*Strain:* B clade HXB2 *HIV component:* Gag**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)**Keywords** Th1**References** Mata *et al.* 2001

- BALB/c and C57BL/6 mice were immunized with *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag.
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm; secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways.
- CD4+ Th1 T-cells mediated the Gag specific immunological protection in mice immunized with Lm-Gag and challenged with vaccinia-Gag.
- Gag-specific CTL may enhance viral clearance via IFN- $\gamma$  secretion, but are not essential for immunity.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** vaccine*Vector/Type:* Listeria monocytogenes *HIV component:* Gag**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)**Keywords** review, Th1**References** Mata & Paterson 2000

- BALB/c and C57BL/6 mice were immunized with *Listeria monocytogenes* (Lm-Gag) expressing HIV-1 HXB2 Gag and mice were challenged with vaccinia expressing Gag.
- *L. monocytogenes* is a gram-positive bacteria that enters the macrophage on phagocytosis and lives in the cytoplasm; secreted *L. monocytogenes* antigens are processed and presented by both class I and class II pathways.
- This article is a review of *L. monocytogenes* biology and its potential as a vaccine vector for HIV, comparing to other vector systems, and discussing CD4+ Th1 T-cell-mediated Gag specific immunological protection in mice and the Gag CTL response.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection, vaccine*Vector/Type:* virus-like particle (VLP) *HIV component:* p17 Gag, p24 Gag**Species (MHC)** human**References** Kelleher *et al.* 1998b

- Immunization of HIV+ people with a p24-VLP virus-like particle did not significantly impact CD4+ lymphocyte count, viral load, or p24 antibody titre.
- Immunization with p24-VLP showed a modest, short-lived increased proliferative response to p24.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection, vaccine

*Vector/Type:* gp120 depleted virus HZ321 (REMUNE(TM)), protein *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus, p24 Gag

**Species (MHC)** human

**References** Maino *et al.* 2000

- 18 HIV-1-seropositive patients with a low frequency or no detectable CD4+ T cell response to HIV-1 antigen received an HIV-1 immunogen consisting of 10 units of native p24 and 100 ug of HZ321, a gp120 depleted antigen.
- Using flow-cytometric methods, HIV-1 specific CD4+ T cells were shown to increase in response to immunization – in many patients significant enhancement was observed after a single immunization.
- The frequency of CD4+ T cells expressing cytokines in response to antigen by FACS was correlated with a lymphoproliferation assay.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Ruiz *et al.* 2000

- Structured treatment interruption in chronically infected patients allowed recovery of p24 Th proliferative responses after HAART therapy discontinuation in 2/12 patients.
- The Th response to p24 was identified during peak viremia in one patient, while in the second it was noted when viremia was controlled after restarting antiviral therapy.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Lori *et al.* 1999

- Ten patients with acute, pre-seroconversion HIV-1 infections were treated with didanosine, indinavir and hydroxyurea – this treatment is associated with normalization of immune parameters.
- A vigorous HIV-specific Th response (stimulation index greater than 8) was observed in 7/8 patients treated before complete WB seroconversion, but in only 1/5 controls treated after seroconversion.
- Vigorous Th responses were detected as early as 34 days after treatment begin.
- Patients treated prior to seroconversion had no loss of naive CD4 T lymphocytes, recovery of up to 35% of the naive CD8 cells in several weeks, and a reduced latent viral reservoir.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, supervised treatment interruptions (STI), Th1

**References** Haslett *et al.* 2000

- 11/22 adult patients on HAART showed strong CD4+ T-cell IFN- $\gamma$  producing Th1 responses to HIV p24.
- The magnitude of the Th1 response correlated with previous interruptions in HAART, suggesting the interruptions primed or boosted the response.
- In contrast, the magnitude of the CD8+ CTL response did not correlate with interruptions in therapy, although a greater breadth in response was associated with interruptions in HAART.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* virus-like particle (VLP) *HIV component:* p17 Gag, p24 Gag

**Species (MHC)** human

**References** Klein *et al.* 1997

- Immunization of HIV+ people with a HIV-1 p17/p24 Ty virus-like particle (p24-VLP) resulted in a marginal, short-lived increased proliferative response to p24 and p17 and a transient elevation in viral load.
- Two of four subjects that received 500 or 1000 ug of p24-VLP had an increase in gag-specific CTL.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** vaccine

*Vector/Type:* gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Moss *et al.* 1998

- Immunization with gp120 depleted HZ321 virus (REMUNE<sup>TM</sup>) triggered an increase in lymphocyte proliferative response to native p24, a clade B virus and clade E viral antigens – Z321 is clade A in env and clade G in gag. Moss *et al.* [1998]

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART

**References** Rosenberg *et al.* 1999

- This paper reviews the role of T-cells in viral control and HIV disease outcome.
- Strong anti-p24 lymphoproliferative responses were found in seven persons who were treated with potent anti-viral therapy during acute HIV-1 infection syndrome.
- This suggests that Th cells are part of the normal response to HIV-1 infection, but their numbers are rapidly diminished by either being infected during the peak viremia or by activation-induced cell death – if peak viremia can be controlled, a robust anti-p24 Th response can be maintained.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Rosenberg & Walker 1998

- Strong Th responses have been found in rare individuals who effectively maintain low viral loads.
- If aggressive anti-retroviral therapy is given prior to sero-conversion, strong helper responses can be maintained.

**HXB2 Location** Gag**Author Location** p17**Epitope****Immunogen** vaccine*Vector/Type:* protein *HIV component:* p17

Gag

**Species (MHC)** mouse**References** Birk *et al.* 1998a

- Different p17 genes derived from the same quasispecies and expressed and purified in *E. coli* primed different Th 1 and Th 2 subsets in mice, depending on their H-2 type.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Schiller *et al.* 2000

- Study of parameters that might influence the performance or reproducibility of clinical Th proliferative assays.
- HIV-1 replication *in vitro* is unlikely to influence the assay.
- Gag proteins including p17 and possibly p7 as well as p24 perform better than p24 alone.
- Frozen samples can be used in T-proliferative assays, but with lower radiolabeled thymidine incorporation.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Pitcher *et al.* 1999

- In contrast to earlier studies suggesting that HIV-1 specific Th responses were eliminated in the early stages of infection in most HIV+ individuals, this paper shows using flow cytometric detection of antigen-induced cytokines that Th-1 CD4+ memory gag-specific Th cells are detectable in most HIV+ subjects.
- Effective anti-viral therapy reduces the frequency of these cells, presumably due to reduced antigenic stimulus.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Plana *et al.* 1998

- Patients from later stages of infection given HAART do not show restoration of HIV-1 specific Th proliferative responses.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Kelleher *et al.* 1998a

- Env and gag Th epitopes were pooled and used to test Th proliferative responses after IL2 therapy – while IL2 therapy causes an increase in CD4+ lymphocyte count, it does not increase HIV-1 specific proliferative responses.

**HXB2 Location** Gag**Author Location** Gag (LAI)**Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* DNA prime with vaccinia boost*Strain:* B clade LAI *HIV component:* Env, Gag**Species (MHC)** macaque**Keywords** Th1, Th2**References** Kent *et al.* 1998

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T-cell immunity than either vaccine alone.
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env – The Th response happened despite a fall in Ab titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced.

**HXB2 Location** Gag**Author Location****Epitope****Immunogen** vaccine*Vector/Type:* DNA, protein, virus-like particle (VLP), ISCOM**Species (MHC)** macaque**Keywords** Th1, Th2**References** Heeney *et al.* 1999

- Ten different vaccine strategies were evaluated for their ability to protect from infection in a rhesus macaque model using a non-pathogenic SHIV challenge.
- Protection correlated with the magnitude of NAb responses, beta-chemokines, and a balanced Th response.
- DNA, protein+adjuvant, VLP and ISCOM vaccines were tested.
- HIV-1/ISCOMS gave the highest NAb titers, Th1 and Th2 responses, was the only vaccine formulation tested with a detectable CTL response, and gave enhanced beta-chemokine production.

**HXB2 Location** Gag**Author Location** Gag/Pol (MN)

**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade MN*HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86**Species (MHC)** chimpanzee**References** Kim *et al.* 1998

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

**HXB2 Location** Gag**Author Location** Gag/Pol (LAI, MN)**Epitope****Immunogen** vaccine*Vector/Type:* canarypox *Strain:* B cladeLAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease**Species (MHC)** human**References** Salmon-Ceron *et al.* 1999

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy uninfected volunteers.

**HXB2 Location** Gag**Author Location** p55 (IIIB)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Zhang *et al.* 2001b

- T-helper cell proliferative responses to HIV p24, p55 and gp120 were tested in 27 patients with HIV infection – vigorous responses directed at Gag were detected in ten patients, but an Env specific response was detected in only one patient.
- Untreated patients showed a negative correlation between plasma viral load and HIV p24-specific T-cell responses, and the responses could be detected after extended HAART therapy with viremia below the detection limit.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, supervised treatment interruptions (STI), kinetics, Th1**References** Carcelain *et al.* 2001

- Repeated structured HAART therapy interruptions (STI) in 3 chronically HIV infected patients induced rapid but transient (< 3 weeks) HIV-1 specific CD4+ Th1 responses concurrently with viral rebound, as measured by proliferation assays and by IFN- $\gamma$  production by CD8-depleted PBMC.
- Kinetics suggest that viral replication leads to rapid destruction of the HIV-specific Th1 cell response.
- HIV-specific CD8+ T-cell responses were delayed relative to the Th1 responses and were not sustained.

**HXB2 Location** Gag**Author Location** Gag**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Blankson *et al.* 2001

- 5/10 chronically HIV infected patients with low CD4+ counts who received HAART therapy and experienced immune reconstitution displayed p24, p17 and p66 T-helper CD4 proliferative responses, in contrast to 0/8 chronically HIV infected patients with high CD4+ counts at the initiation of antiretroviral treatment.
- This surprising result could be due to the low CD4 nadir patients being more likely to have thymic regeneration or a peripheral expansion of T cells.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Angel *et al.* 2001

- Prolonged viral suppression resulting from potent antiretroviral therapy allowed a T helper response to Gag p24 and PHA to develop in many HIV+ patients.
- At baseline, 2/41 (4.9%) subjects had a proliferative response to Gag p24, and 7/41 (17.1%) had a response to PHA, but by week 72 of therapy, 53% had a detectable response to p24 and 94% to PHA.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Blazevic *et al.* 2000

- Prolonged viral suppression resulting from potent antiretroviral therapy did not allow an HIV T helper response to p24 or gp160, but Th proliferative responses to influenza, alloantigen, and PHA did develop in many HIV+ patients, and asymptomatic patients had stronger and more frequent Th response recovery than AIDS patients.

**HXB2 Location** Gag**Author Location** Gag (SF2)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, acute/early infection**References** Altfeld *et al.* 2001b

- Therapy provided during acute infection resulted in a narrower CTL response, stronger T help response, and a less diverse viral population than was seen in individuals treated during chronic infection.

- The breadth and specificity of the CTL response was determined using Elispot by studying 19 individuals with pre-seroconversion therapy (Group 1), 11 individuals with primary infection but post-seroconversion therapy (Group 2), and 10 individuals who responded to HAART given during chronic infection (Group 3), using 259 overlapping peptides spanning p17, p24, RT, gp41, gp120 and Nef.
- Individuals who were given HAART during acute or early in infection had significantly stronger proliferative responses than individuals who were chronically infected.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV-specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV-specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.
- In 3/4 responders tested p24 gave the strongest T helper response.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** vaccine

*Vector/Type:* gp120 depleted whole killed virus *Strain:* AG recombinant HZ321 *HIV component:* virus *Adjuvant:* Complete Freund's Adjuvant (CFA), CpG immunostimulatory sequence (ISS)

**Species (MHC)** rat

**References** Moss *et al.* 2001

- Different HIV strains were used for different regions: subtype A env, subtype G gag
- Lewis rats simultaneously immunized with HIV-1 antigen and with immunostimulatory sequences CpG had increased Th proliferative responses, but when CpG was given as a prime prior to the injection of HIV-1 antigen it was not as effective.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** vaccine

*Vector/Type:* gp120 depleted whole killed virus *Strain:* AG recombinant HZ321 *HIV component:* virus *Adjuvant:* Complete Freund's Adjuvant (CFA), CpG immunostimulatory sequence (ISS)

**Species (MHC)** rat

**References** Moss *et al.* 2000

- Different HIV strains were used for different regions: subtype A env, subtype G gag

- Lewis rats co-immunized with HIV-1 antigen in Freund's and with immunostimulatory sequences CpG stimulated increased IFN- $\gamma$  expressing CD4+ and CD8+ T cells and anti-p24 antibodies relative to antigen in Freund's without CpG.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression, Th1

**References** Kalams *et al.* 1999a

- The strength of p24 specific Gag proliferative responses (SIs) were inversely correlated with viral load in 21 ARV naive patients. The responses were Th1, IFN- $\gamma$  producing. Proliferative responses against gp160 were rarely observed (only 4 cases).
- Gag specific CTL levels were correlated with Gag proliferative responses but were not correlated with viral load. 8 subjects lacked p24 specific Gag proliferative responses, and 4/8 had no CTLp to any HIV-1 antigen tested.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, review, rate of progression

**References** Kalams & Walker 1998

- This paper reviews the role of specific T cell help in many viral infections, and covers the interplay between Th, CTL and survival, and discusses briefly advantages of HAART during acute HIV infection to prevent the early decimation of the Th response in HIV infections.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression, Th1, Th2

**References** Wilson *et al.* 2000b

- Dysfunction of HIV-1 specific proliferative responses, but not responses to other antigens, is evident in HIV-1 progressive disease.
- Vigorous HIV-1 specific responses to p24, Nef and gp120 with SI between 8-99 were seen in 6/7 long term non-progressors (LTNP), the seventh had a borderline responses. IL-2 production was seen in all cases, and IL-4 production was also evident many responses.
- None of the progressors (0/5) had HIV-1 specific proliferative responses, or IL-2 or IL-4 induction.
- Non-HIV antigens (cytomegalovirus, PPD, Staphylococcus enterotoxin B, tetanus toxoid) gave similar responses in HIV-1 + LTNP, progressors, and HIV-1 controls.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression, Th1

**References** Alatrakchi *et al.* 2002

- LTNP co-infected with HCV and HIV showed higher frequencies of Th1 response to both HIV-1 p24 and HCV antigens.
- HIV-1 CD4 Th1 responses in untreated LTNP were inversely correlated with viral load.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART

**References** Lange *et al.* 2002

- Cross-sectional study compares CD4 T-cell count and age matched untreated HIV-1 + patients (N = 14) with patients undergoing HAART therapy (N = 14).
- The fractions of naive and memory T-cells were comparable for both groups, as were proliferative responses to non-HIV antigens. Lymphocyte proliferation responses to HIV-1 p24 were of greater magnitude in the group treated with HAART (5/10 had SI >10, versus 1/12 in the untreated group), suggesting that ongoing viral replication impairs the anti-Gag response, and the response can be improved and restored through HAART.
- DTH responses to recall antigens were tested, and responses to *C. albicans* and *Trichophyton* were comparable in both treated and untreated patients, although patients on therapy had higher responses to mumps.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, subtype comparisons, escape, acute/early infection

**References** Fidler *et al.* 2002

- 37/45 patients with primary HIV infection underwent a short course of antiretroviral therapy (SCART). 29/37 patients received triple ART therapy and eight patients received four ART drugs. Initiation of SCART was effective in controlling HIV replication by ten weeks in all patients and preserving CD4+ T cell responses for up to 64 weeks after therapy.
- No induction of drug escape mutations was observed, although two individuals had escape mutations in their infecting virus at baseline.
- 34 UK infected patients were clade B infected. 11/45 subjects had non-UK acquired HIV infection, 2 were clade A, 1 was A/E, 1 was C, 1 was "untypable", the rest were B.
- Recombinant HIV-1 derived gp120, p24, p66 and overlapping peptide pools spanning Tat and Nef were employed to measure CD4 T-cell frequencies in ELISPOT assays. The strongest preservation of T helper responses 12 weeks off SCART was seen for p24-specific CD4+ T-cell responses.
- 6/8 of the untreated individuals were tested for CD4+ T-cell responses. 1 had no detectable response. 1 had detectable responses to all HIV-1 proteins tested at baseline, but this narrowed to p24 and gp120, then became undetectable by 52

weeks. 3 had detectable and persistent responses, but only to p24.

- Post-therapy, the average spot forming cells for all proteins tested in 17/37 with 24 weeks of follow up had not declined, although the plasma viral RNA was increasing. SFU using p24 were measurable following SCART and preserved at levels comparable to baseline.

**HXB2 Location** Gag

**Author Location**

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP)

*Strain:* B clade IIIB *HIV component:*

p17 Gag, p24 Gag *Adjuvant:* aluminum hydroxide

**Species (MHC)** human

**Keywords** rate of progression

**References** Klein *et al.* 1997; Lindenburg *et al.* 2002

- HIV-1 p17/p24:Ty virus-like particles therapeutic vaccination of 56 HIV-1 infected patients had no effect on disease progression, AIDS and CD4+ T-cell decline in a longitudinal study, despite some evidence suggesting it can enhance Th anti-Gag proliferative responses in HIV+ individuals Klein *et al.* [1997]

**HXB2 Location** Gag

**Author Location** p24 (NY5)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART, supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection, cross-presentation by different HLA, early treatment

**References** Norris *et al.* 2001

- Gag-specific CD4+ helper T-cell clones were derived from 1 LTNP (CTS-01) and 3 individuals given therapy during acute infection, 2 before (AC-01 and AC-36) and 1 after (AC-25) STI.
- The immunodominant response in LTNP CTS-01 was to peptide 9, and 9/10 clones derived from this patient reacted with it. Three, two, and one clones were obtained from the 3 patients given therapy. These 6 clones all reacted with different p24 peptides, and all had peptide induced proliferative responses, IFN- $\gamma$  production, and cytotoxic responses. The implications of cytotoxic responses in CD4+ T-helper cells are discussed.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART

**References** Palmer *et al.* 2002

- CD4+ T cell proliferative responses from 33 HIV-1 infected patients with HAART suppression were compared to 19 patients with active viral replication (HAART failures and HAART naive). Patients with HAART suppression showed stronger p24- and p66-specific proliferative responses compared to patient groups with active HIV-1 replication, suggesting active viral replication *in vivo* specifically reduces proliferation responses.
- No differences in the frequency of HIV-specific CD4+ T-cells that were positive for cytokine secretion in a flow cytometry assay were found in the HAART suppressed group versus the group with active viral replication.

**HXB2 Location** Gag

**Author Location** p24 (SF2)

**Epitope**

**Subtype** B, G

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression, Th1, Th2

**References** Imami *et al.* 2002b

- 70 patients with chronic disease progression, 10 clinical non-progressors, and 3 immunologically discordant progressors (individuals who controlled viremia but had progressive CD4+ T-cell decline) were analyzed for their T-helper cell responses to p24 and cytokine profile.
- SF2 p24 20mer peptides overlapping by 10 were used to assess the response in the different groups. At least 1/10 and up to 7/10 nonprogressors had a proliferative response with every one of the 22 p24 overlapping peptides. All peptides produced an IL-2 (Th1) response in at least one of the 10 non-progressors. IL-4 (Th2) responses were strong, but somewhat less comprehensive as 6/22 peptides elicited no IL-4 production, and fewer IL-4 responses were seen per peptide. In contrast, only 1/10 progressors had a clear proliferative and IL-2 response to 2/22 peptides, and neither one made an IL-4 response.
- The results taken together suggest that a balanced Th1/Th2 response to HIV is important for viral control in long-term non-progression.
- One immunologically discordant progressor became symptomatic while on the study. He showed a rapid decline in proliferative activity at that point, and a shift from a Th1 to a Th2 IL-4 producing response.

**HXB2 Location** Gag

**Author Location** (BRU)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* B clade BRU *HIV component:* virus *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse

**References** Haas *et al.* 1991

- Of 5 mouse inbred lines tested: DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.

- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.

**HXB2 Location** Gag

**Author Location** Gag (III-B)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade IIIB

*HIV component:* Gag

**Species (MHC)** mouse

**Donor MHC** H-2<sup>d</sup>

**Keywords** vaccine-specific epitope characteristics, Th1

**References** Bojak *et al.* 2002a

- Codon-optimized gag gene DNA vaccines were compared to wild type by vaccination of BALB/c mice. Codon optimized DNA gave a Th1 polarized Th response, a strong antibody response that persisted from more than 20 weeks, and CTL responses, while wild-type DNA induced weak and inconsistent immune responses.

**HXB2 Location** Gag

**Author Location** Gag (MN)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** Cytokine production, proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** HAART, ART, acute/early infection

**References** Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymphoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* gp120 depleted virus HZ321

(REMUNE(TM)), protein *Strain:* AG re-

combinant HZ321 *Adjuvant:* Incomplete

Freund's Adjuvant (IFA)

**Species (MHC)** human

**Assay type** Cytokine production, proliferation, T-cell Elispot

**Keywords** HAART, ART, supervised treatment interruptions (STI), immunotherapy

**References** Moss *et al.* 2003

- Structured treatment interruptions (STIs) were compared in individuals that had been given prior therapeutic vaccines, and those that had not. Therapeutic immunization increased gag p24 stimulated proliferative responses and MIP-1 $\beta$  responses prior to STIs, although total CD4 counts viral RNA levels were unchanged. Proliferative responses and chemokine induction in the vaccinated group correlated with the control of viremia during subsequent STIs.

**HXB2 Location** Gag**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** proliferation, T-cell Elispot, Intracellular cytokine staining**Keywords** supertype**References** Papasavvas *et al.* 2003

- Children with full or partial viral suppression along with stable CD4+ T cell counts had significantly increased levels of anti-HIV CD4+ T cell proliferative responses, and decreased CD38+ T-cells.
- Preservation of high levels of CD4+ T-cells was associated with a high percentage of CD4+ naive T-cells relative to memory T-cells.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection, vaccine*Vector/Type:* gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *Adjuvant:* Incomplete Freund's Adjuvant (IFA)**Species (MHC)** human**Assay type** proliferation, T-cell Elispot, Delayed-type hypersensitivity (DTH)**Keywords** HAART, ART, immunotherapy**References** Robbins *et al.* 2003

- Augmented Th cell responses to Gag p24 were seen in five out of five chronically infected individuals who had virological control with HAART, after therapeutic immunization with REMUNE (gp120 depleted inactivated virus). The magnitude of responses ranged from a 5- to 200-fold increase, with fluctuation in magnitude over time.
- There was no change in the magnitude and breadth of CTL responses, CD4 counts or percentages, or DTH responses.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Donor MHC** A1, A2, B44, B8, DR15, DR4; LTNP S24: A11, A2, B55, B57, DR13, DR4; LTNP C135: A1, A33, B50, B57, DR13, DR7**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining**Keywords** rate of progression, immunodominance**References** Wang *et al.* 2002a

- A 51 year old male, infected presumably in 1988, diagnosed seropositive in 1993, has remained asymptomatic and is a long term non-progressor. He had very low proviral copy number in his PBMCs with high levels of G-A hypermutation, resulting in multiple stop codons, and viral replication was not evident. He was heterozygous for the CCR5 delta 32 allele, and has undergone a variety of treatments through the years. T cell responses in this patient and in two additional LTNP were described, and this patient had particularly intense CD4+ Th responses.
- PBMC from this patient resisted infection from CCR5, CXCR4 and dual-tropic HIV-1 strains. Purified CD4+ T cells became infected, however, without detectable cytopathic effect. CD8+ T cells were shown to protect PBMCs from infection, and this protection was not mediated by IFN $\gamma$ . Undefined CD8 T-cell secreted factors were stimulated by Gag, Pol and Nef genes introduced into target cells with vaccinia and processed through a class I pathway were responsible for the protective effect. This factor resembled CAF, the CD8+ cell antiviral factor described in Mackewicz and Levy (ARHR 8:1039, 1992)
- The CD4+ and CD8+ T-cell populations were both strongly skewed toward the CD45RO+ phenotype, many of which were terminally differentiated, CD28-, and expressed the activation markers CD38+ and HLA-DR+. Cell turnover, however, wasn't much elevated as measured by apoptosis or Ki-67+ and Bcl-2 dim expression.
- Vigorous p24-specific Th proliferative responses were observed, and 50% of CD4+ T-cells proliferated in response to p24 Gag, an extraordinary percentage. Responses were also detected against other regions in Gag, gp120 and Nef. It remains unclear how such vigorous Th responses are maintained with undetectable ongoing viral replication.
- Strong CD4+ T-cell IFN $\gamma$  Elispot responses were mapped to many peptides in Gag for this patient. T-cells from two other LTNP were tested here, and they did not react with as many Gag peptides as the main study subject of the paper. NIH reference Gag peptide set was used, but the sequences of the reactive peptides and the precise strain was not indicated in the paper, so we could not record them in the database.
- CD8+ T cell Elispot responses to Gag, Env, Nef, and Pol were detected as well, although CTL were not prominent, consistent with undetectable viremia.
- This subject had strong NAb responses when tested using the X4 primary isolate 228 200.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection**Species (MHC)****Assay type** proliferation**Keywords** HAART, ART**References** Sullivan *et al.* 2003

- Lymphoproliferative responses to HIV antigens p24, gp120 and Nef were enhanced in eight patients who were switched from protease inhibitors to non-nucleoside reverse transcriptase inhibitors.



- HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Assay type** Cytokine production, proliferation  
**Keywords** HAART, ART  
**References** Hardy *et al.* 2003
- Upon initiating HAART, CD4+ T cell proliferative responses in 36 patients were restored to specific antigens, mitogens, and IL-2. Restored recall responses were largely to persistent antigens, and not to HIV-1 or new antigens, and recall responses were associated with IL-2, not IL-4 production.

- HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Immunogen** HIV-1 and HCV co-infection  
**Species (MHC)** human  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** HAART, ART, Th1  
**References** Alatrakchi *et al.* 2004
- Treatment with IFN $\alpha$  and ribavirin induced a threefold decrease of type 1 T-helper cell frequencies specific for HIV (p24) and CMV in HIV/HCV co-infected patients undergoing HAART therapy, suggesting this therapy might negatively impact viral-specific immune responses.

- HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Spain  
**Assay type** proliferation  
**Keywords** HAART, ART, supervised treatment interruptions (STI)  
**References** Plana *et al.* 2004
- Study evaluated the dynamics of CD4+ and CD8+ T-cell responses during 4 cycles of STI in 45 patients, who had early-stage, chronic HIV-1 infection. Lymphoproliferative responses (LPRs) increased between the beginning of the first STI cycle through the 4th STI, but then decreased. Viral load at the end of the 4th STI was inversely correlated with p24 LPRs, but the LPRs were transient and after 12 weeks no longer were correlated with low viral load.
  - STIs can boost CTL and LPR responses, but the lack of durable T-helper responses leads to lack of long term viral control.

- HXB2 Location** Gag  
**Author Location**  
**Epitope**  
**Subtype** CRF02\_AG  
**Immunogen** HIV-1 or HIV-2 infection  
**Species (MHC)** human  
**Country** Senegal  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** rate of progression, variant cross-recognition or cross-neutralization

**References** Zheng *et al.* 2004

- Gag, Env, Tat, and Nef-specific T-cell responses were evaluated in 68 HIV-1 and 55 HIV-2 infected drug naive, generally asymptomatic, infected Senegalese patients.
- HIV-1 peptides were derived from HIV-1 CRF-02 (HIV-1 A/G, AJ251056) and HIV-2 peptides spanning HIV-2 ROD (M15390).
- Gag specific responses dominated in both groups, but overall magnitude and frequencies did not correlate with viral load or CD4 counts. CD4+ Helper T-cell responses were found in only 8% of HIV-1 + people, but in 48% of HIV-2 + people, suggesting helper T cell responses may contribute to improved control of viremia in HIV-2 infected patients. Lower viral load was associated magnitude of T-cell responses in HIV-1 infection only when the T-cell responses were measured for cross-reactivity with HIV-2.

- HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Subtype** A, AG, B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Cote D'Ivoire  
**Assay type** Cytokine production, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** HIV exposed persistently seronegative (HEPS)

**References** Jennes *et al.* 2004

- Env(gp120)- and Gag(p24)-specific T helper responses were compared between HIV-exposed seronegative (ESN) and seropositive female sex workers in Africa (Abidjan, Cote d'Ivoire).
- HIV-specific CD4+ T cells were detected in both study groups; low level EliSpot responses were found in 8/40 ESN sex workers. The presence of HIV specific CD4+ T-cells was detected by flow cytometry in 3/8 (38%) in the ESN group, was associated with the frequency and not with the duration of HIV exposure. The ESN responses were detected in women with more clients on the previous working day and more exposures per month.
- B subtype peptides were used to probe these responses because of availability, however the predominant clades circulating in the area are A and CRF02.

- HXB2 Location** Gag  
**Author Location** Gag  
**Epitope**  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Netherlands  
**Assay type** proliferation, Intracellular cytokine staining  
**References** Jansen *et al.* 2006

- Functional CD4+ T cells were compared in long-term asymptomatic individuals (LTA) and progressors to AIDS. Gag-specific CD4+ T cells producing IL-2 or IFN- $\gamma$  were lost in progressors late in infection.

- HXB2 Location** Gag  
**Author Location**

**Epitope****Immunogen** vaccine*Vector/Type:* DNA with CMV promotor  
*Strain:* B clade HXB2, B clade NL43, A clade 92RW020, C clade 97ZA012 *HIV component:* Env, Gag, Nef, Pol**Species (MHC)** human**Country** United States**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay**Keywords** therapeutic vaccine**References** Catanzaro *et al.* 2006

- 14 volunteers uninfected with HIV completed a set of injections with a 6-plasmid DNA vaccine encoding EnvA, EnvB, EnvC, and subtype B Gag, Pol, and Nef. CD4 and CD8 T cell responses to Env and Gag were most frequently detected.
- For Gag, 12/14 subjects showed a positive CD4+ T cell response by ICS.

**HXB2 Location** Gag**Author Location****Epitope****Immunogen** vaccine*Vector/Type:* adenovirus type 5 (Ad5) *HIV component:* Env, Gag *Adjuvant:* Cholera toxin (CT)**Species (MHC)** macaque**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other**Keywords** vaccine antigen design**References** Mercier *et al.* 2007

- 3 rhesus macaques were given oral immunizations with an enteric-coated mixture of adenoviral vectors expressing HIV-1 gag and a string of conserved env peptides representing broadly cross-reactive CD4+ and CD8+ epitopes. The macaques were boosted intranasally with a mixture of 6 HIV-1 envelope peptides plus cholera toxin adjuvant.
- The immunizations increased cellular immune responses, including antigen-specific IFN $\gamma$ -producing CD4+ and CD8+ effector memory T cells in the intestine. After only the oral immunization, there were no EliSpot responses to env peptides or to gag. After the intranasal boost, EliSpot responses against env peptides and against inactivated HIV were markedly increased, but gag responses were not.

**HXB2 Location** Gag**Author Location** Gag (HXB2)**Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* DNA prime with vaccinia boost  
*Strain:* B clade HXB2 *HIV component:* Gag**Species (MHC)** mouse**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Chromium-release assay**Keywords** vaccine-induced epitopes, Th1**References** Arruda *et al.* 2006

- p55 Gag cellular trafficking of two chimeras (DNA plasmid with either lysosomal-associated membrane protein LAMP/gag or human dendritic cell CD-LAMP/gag) was studied in mice. Both produces potent T and B cell immune responses, but DC-LAMP produces stronger Th1 response. The chimeras produces also significant responses to cryptic epitopes that were not recognized after immunization with native gag DNA.

**HXB2 Location** Gag**Author Location** p24**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Country** South Africa**Assay type** proliferation, Intracellular cytokine staining**References** Day *et al.* 2006

- PD-1 (inhibitory receptor programmed death) expression on CD8 and CD4 cells was studied. There was a positive correlation with viral load and inverse correlation with CD4 T cell count, and blockage of PD-1 pathway augmented CD4 and CD8 T cell function.

**HXB2 Location** Gag**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Country** Kenya**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining**Keywords** responses in children, rate of progression**References** Chakraborty *et al.* 2005

- A study of long-term surviving children in Kenya revealed CD8 T-cell responses in all progression groups. The most striking attribute of long term surviving children was strong CD4 T-cell responses, which may be significant in delaying disease progression.
- Preservation of Gag-specific CD4+ Th responses have been described for adult non-progressors, and this study described similar responses for slow and non-progressing children.

**HXB2 Location** Gag**Author Location****Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade**Species (MHC)** macaque**Assay type** Intracellular cytokine staining**Keywords** subtype comparisons, vaccine antigen design**References** Smith *et al.* 2005

- Macaques were immunized with a clade B HIV vaccine and tested for responses to pools of clade B and A/G Env and Gag peptides. While CD4 responses were more frequent than CD8 responses, higher cross-clade responses were found for CD8

responses. The authors suggest that the better cross-clade reactivity of the CD8 responses reflects the size difference between CD8 and CD4 epitopes; the smaller CD8 epitopes provide a smaller target for mutation.

- All 5 pools of B Env and Gag peptides stimulated CD4 responses, while only 2 pools of A/G peptides stimulated responses, suggesting that 1 or 2 out of 5 CD4 epitopes were cross-reactive.

**HXB2 Location** Gag

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** Intracellular cytokine staining

**Keywords** acute/early infection

**References** Zaunders *et al.* 2005

- In 6/7 patients with very early HIV infection, CD4+ T cells producing IFN-g in response to Gag peptides were readily detected, and most CD4+ T cells were CCR5+CD38+++. In PHI subjects with later presentation, antigen specific CD4+ T cells could not be readily detected, coinciding with a lower level of CCR5+CD38+++ CD4+ T cells.

### III-B-6 Protease Helper/CD4+ T-cell epitopes

**HXB2 Location** Protease (7–21)

**Author Location** Protease (7–21 clade B consensus)

**Epitope** QRPLVTIKIGGQLKE

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB1\*0101, DRB1\*1101, DRB1\*1501, DRB5\*0101)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is QRPLVTIKIGGQLKE, shorter LVTIKIGGQ peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** Protease (49–72)

**Author Location**

**Epitope** GIGGFIKVRQYDQILIEICGKKAI

**Epitope name** HIV-VAX-1048

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 3/13 US test subjects responded to this 23-mer by CD4 Elispot assay. The core computer-predicted peptide was VRQY-DQILL.

**HXB2 Location** Protease (74–96)

**Author Location**

**Epitope** TVLVGPTPVIIGRNLLTQIGCT

**Epitope name** HIV-VAX-1046

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 3/13 US test subjects responded to this 23-mer by CD4 Elispot assay. The core computer-predicted peptide was PVNI-IGRNLL.

**HXB2 Location** Protease (80–94)

**Author Location** Protease (80–94 clade B consensus)

**Epitope** TPVNIIGRNLLTQIG

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB1\*0101, DRB1\*1101, DRB1\*1302, DRB1\*1501)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide is TPVNIIGRNLLTQIG, shorter VNIIGRNLLTQ peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

## III-B-7 RT Helper/CD4+ T-cell epitopes

- HXB2 Location** RT (36–52)  
**Author Location** RT (36–52 BRU)  
**Epitope** EICTEMEKEGKISKIGP  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** De Groot *et al.* 1991
- 9 out of 17 humans can make strong IL2 responses to this epitope.
- HXB2 Location** RT (38–52)  
**Author Location** RT (38–52 BRU)  
**Epitope** CTEMEKEGKISKIGP  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* RT  
**Species (MHC)** mouse (H-2<sup>k</sup>)  
**References** De Groot *et al.* 1991
  - T-cells from RT immunized mice have enhanced proliferative response with peptide.

**HXB2 Location** RT (39–53)  
**Author Location** RT (194–208)  
**Epitope** TEMEKEGKISKIGPE  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** Manca *et al.* 1995a
  - Protein priming induced T-cells that recognize peptide, 4 clones from a single donor recognized this peptide.

**HXB2 Location** RT (48–62)  
**Author Location** RT (48–62 BRU)  
**Epitope** SKIGPENPYNTPVFA  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* RT  
**Species (MHC)** mouse (H-2<sup>k</sup>)  
**References** De Groot *et al.* 1991
  - T-cells from RT immunized mice have enhanced proliferative response with peptide.

**HXB2 Location** RT (62–77)  
**Author Location** RT (62–77 BRU)  
**Epitope** AIKKKDSTKWRKLVDF  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* RT  
**Species (MHC)** mouse (H-2<sup>k</sup>)  
**References** De Groot *et al.* 1991
  - T-cells from RT immunized mice have enhanced proliferative response with peptide.

**HXB2 Location** RT (88–102)  
**Author Location** RT (88–102 BRU)  
**Epitope** WEVQLGIPHPAGLKK  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* RT  
**Species (MHC)** mouse (H-2<sup>I4</sup>)

- References** De Groot *et al.* 1991
- T-cells from RT immunized mice have enhanced proliferative response with peptide.
- HXB2 Location** RT (124–138)  
**Author Location** Pol (303–317)  
**Epitope** FRKYTAFTIPSINNE  
**Epitope name** Pol 303  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR supermotif)  
**Keywords** subtype comparisons  
**References** Wilson *et al.* 2001
  - Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
  - This epitope binds seven HLA-DR alleles: DRB1\*0901, DRB1\*0802, DRB1\*0701, DRB1\*0405, DRB1\*0401, DRB1\*1501 and DRB1\*0101, with an IC<sub>50</sub> threshold below 1,000 nM.
  - This epitope sequence is conserved in 68% of clade B isolates.
  - 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

**HXB2 Location** RT (124–138)  
**Author Location** RT (303–317)  
**Epitope** FRKYTAFTIPSINNE  
**Epitope name** Pol1  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR supermotif)  
**Country** United Kingdom  
**Assay type** proliferation, Intracellular cytokine staining  
**Keywords** supertype, rate of progression  
**References** Boaz *et al.* 2003
  - Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
  - Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN  $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.

**HXB2 Location** RT (124–138)  
**Author Location** Pol (303–317)  
**Epitope** FRKYTAFTIPSINNE  
**Epitope name** Pol 303  
**Immunogen** vaccine  
*Vector/Type:* DNA with CMV promotor, peptide *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (I-Ab and HLA-DR)

**Donor MHC** H-2b**Keywords** vaccine-specific epitope characteristics, immunodominance**References** Livingston *et al.* 2002

- 4 Th HIV epitopes presented by HLA-DR molecules were identified that also could be presented by murine class II molecule I-Ab, enabling testing of vaccine strategies in H-2b mice.
- Responses to pooled peptides, polyepitope peptides in a linear construct or in a branched MAP construct, and a DNA polyepitope construct with a CMV promoter were compared. A linear arrangement in polyepitope construct created a junctional epitope that could be disrupted with the addition of GPGPG spacers. The linear polyepitope construct with the GPGPG spacer worked well in terms of eliciting responses to all 4 peptides, using either DNA or protein for the vaccination.

**HXB2 Location** RT (133–147)**Author Location** RT (133–147 BRU)**Epitope** PSINNETPGIRYQYN**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade BRU*HIV component:* RT**Species (MHC)** mouse (H-2<sup>i5</sup>, H-2<sup>k</sup>)**References** De Groot *et al.* 1991

- T-cells from RT immunized mice have enhanced proliferative response with peptide.

**HXB2 Location** RT (144–158)**Author Location** RT (144–158 BRU)**Epitope** YQYNVLPQGWKSPA**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade BRU*HIV component:* RT**Species (MHC)** mouse (H-2<sup>i4</sup>)**References** De Groot *et al.* 1991

- T-cells from RT immunized mice have enhanced proliferative response with peptide.

**HXB2 Location** RT (156–170)**Author Location** Pol (335–349)**Epitope** SPAIFQSSMTKILEP**Epitope name** Pol 596**Immunogen** HIV-1 infection**Species (MHC)** human (DR supermotif)**Keywords** subtype comparisons**References** Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds nine HLA-DR alleles: DRB1\*0101, DRB1\*1501, DRB1\*0405, DRB1\*1101, DRB1\*1302, DRB1\*0701, DRB1\*0901, DRB5\*0101 and DRB3\*0101, with an IC<sub>50</sub> threshold below 1,000 nM.
- This epitope sequence is conserved in 79% of clade B isolates.
- 7/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

**HXB2 Location** RT (156–170)**Author Location** RT (335–349)**Epitope** SPAIFQSSMTKILEP**Epitope name** Pol2**Immunogen** HIV-1 infection**Species (MHC)** human (DR supermotif)**Country** United Kingdom**Assay type** proliferation, Intracellular cytokine staining**Keywords** supertype, rate of progression**References** Boaz *et al.* 2003

- Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naïve.
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN  $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.
- Pol2 was 1 of 3 peptides that had a negative correlation between absolute number of responding cells and viral load.

**HXB2 Location** RT (156–170)**Author Location** Pol (335–449)**Epitope** SPAIFQSSMTKILEP**Epitope name** Pol 335**Immunogen** vaccine*Vector/Type:* DNA with CMV promotor, peptide *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (I-Ab and HLA-DR)**Donor MHC** H-2b**Keywords** vaccine-specific epitope characteristics, immunodominance**References** Livingston *et al.* 2002

- 4 Th HIV epitopes presented by HLA-DR molecules were identified that also could be presented by murine class II molecule I-Ab, enabling testing of vaccine strategies in H-2b mice.
- Responses to pooled peptides, polyepitope peptides in a linear construct or in a branched MAP construct, and a DNA polyepitope construct with a CMV promoter were compared. A linear arrangement in polyepitope construct created a junctional epitope that could be disrupted with the addition of GPGPG spacers. The linear polyepitope construct with the GPGPG spacer worked well in terms of eliciting responses to all 4 peptides, using either DNA or protein for the vaccination.

**HXB2 Location** RT (171–189)**Author Location** Pol (171–189 HXB2)**Epitope** FRKQNPDIYIYQMDDLIV**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human (DR0101)**Assay type** Cytokine production, proliferation, Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$

**Keywords** HAART, ART, supervised treatment interruptions (STI)

**References** Iyasere *et al.* 2003

- Fifteen patients receiving HAART with strong CD4+ proliferative responses to HIV antigens while on therapy were examined, to see the effects of viremia on these responses during treatment interruptions. Increased viremia occurred in 12/15 patients during at least one treatment interruption. Anti-HIV proliferative responses were inhibited during viremia, but IFN $\gamma$  production to Gag, Pol, and Nef peptide pools were maintained.
- IL-2 production diminished during viremia, and exogenous IL-2 revived *in vitro* proliferation of HIV-specific T-cells to Gag or Pol DR0101 epitopes in a tetramer, as well as Gag-specific total CD4 T-cell responses.

**HXB2 Location** RT (171–190)

**Author Location** RT (171–190 HXB2)

**Epitope** FRKQNPDIYQYMDLTVG

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR1, DR2 or DR3, DR4 and DR7)

**Keywords** Th1

**References** van der Burg *et al.* 1999

- T-cells specific for this epitope from the three donors were stimulated when presented with target cells pulsed with whole RT, indicating that the peptide is naturally processed for multiple HLA-DR molecules.
- Epitope binds to HLA-DR1, -DR2, -DR3, -DR4, and DR7, and can elicit Th1 cells that recognize peptide, protein, and HIV pulsed stimulator cells in the context of DR1, 2 or 3, 4 and 7 – these HLA types cover more than half of the general population.

**HXB2 Location** RT (171–190)

**Author Location** RT (171–190 HXB2)

**Epitope** FRKQNPDIYQYMDLTVG

**Subtype** B

**Immunogen** HIV-1 infection, *in vitro* stimulation or selection

**Species (MHC)** human (DR1, DR2, DR3, DR4, DR7)

**Keywords** binding affinity, cross-presentation by different HLA, Th1

**References** van der Burg *et al.* 1999

- The goal of this study was to identify Th epitopes that could be cross-presented by multiple class II HLA molecules. 5 RT peptides were identified that could bind to more than one HLA class II protein, and but only 2/5 could stimulate strong proliferation responses in PBMC derived from multiple healthy donors.
- This highly conserved epitope binds with high affinity to HLA-DR1, -DR2, -DR3, -DR4, and -DR7 but not HLA-DR5, and stimulated proliferation in 3/3 PBMC individuals with the appropriate HLA alleles.
- This epitope was able to be naturally processed in protein pulsed stimulator cells, and responding clones had a Th1 cytokine profile.
- This epitope is highly conserved and spans the highly conserved YMDD motif, and showing only minor variability in clades A, B, and D.

**HXB2 Location** RT (174–196)

**Author Location**

**Epitope** QNPDIYQYMDLTVGSDLEIG

**Epitope name** HIV-VAX-1055

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 4/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was YQYMDLTV.

**HXB2 Location** RT (175–197)

**Author Location**

**Epitope** NPEIYQYMDLTVGSDLEIGQ

**Epitope name** HIV-VAX-1051

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 2/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was YQYMDLTV.

**HXB2 Location** RT (195–209)

**Author Location** RT (IIIB)

**Epitope** IGQHRTKIEELRQHL

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Protein priming induced T-cells that recognize peptide.

**HXB2 Location** RT (196–215)

**Author Location** RT (351–370)

**Epitope** GQHRTKIEELRQHLLRWGLT

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995a

- Protein priming induced T-cells that recognize peptide, 4 clones from a single donor recognized this peptide.

**HXB2 Location** RT (249–263)

**Author Location** RT (249–263)

**Epitope** KDSWTVNDIQKLVGK

**Epitope name** RT2

**Immunogen** vaccine, *in vitro* stimulation or selection

*Vector/Type:* HIV-1 peptide in filamentous bacteriophage major coat protein *HIV component:* RT

**Species (MHC)** human (DR5)

**Keywords** epitope processing

**References** De Berardinis *et al.* 2000

- Phage display of the CTL epitope, ILKEPVHGV coupled with T helper epitope KDSWTVNDIQKLVGK, elicited specific CTL responses in PBMC from HIV negative individuals and *in vivo* in immunization of HLA-A2 transgenic mice.
- Bacteriophage presentation of peptides is generally used for stimulation of antibodies, and this novel discovery of CTL epitope processing and presentation suggests new possibilities for these vectors.
- HIV-1 peptides were displayed in filamentous bacteriophage fd virion major coat protein pVIII.

**HXB2 Location** RT (249–263)

**Author Location** RT (249–263)

**Epitope** KDSWTVNDIQKLVGK

**Epitope name** pep23

**Immunogen** vaccine, *in vitro* stimulation or selection

*Vector/Type:* peptide presented on icosahedral protein scaffold *HIV component:* RT  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human, transgenic mouse (DR5)

**Assay type** Cytokine production, T-cell Elispot, Th support of CTL response

**References** Domingo *et al.* 2003

- A virus-like protein scaffold, called E2DISP, derived from pyruvate dehydrogenase multienzyme from *Bacillus stearothermophilus* has been engineered to display 60 copies of one or more epitopes on a single molecule. An E2DISP scaffold which displayed pep23, a 15-residue B and T helper epitope from the reverse transcriptase of HIV-1 elicited a T-helper response *in vitro*.
- The E2DISP scaffold displaying pep23 to stimulate a Th responses, and peptide RT2, which is a CTL epitope from HIV-1 reverse transcriptase, was able to elicit a CD8+ T cell response *in vitro* and in a vaccinated HLA-A2 transgenic mouse. Thus the E2DISP scaffold allows cell-entry and access to the class I and class II processing pathways.
- The Th response in vaccinated mice was also able to support Pep23 specific IgG response.

**HXB2 Location** RT (249–263)

**Author Location** RT (248–262)

**Epitope** KDSWTVNDIQKLVGK

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (DR5-11.01)

**Donor MHC** DR5, DR6

**Assay type** proliferation

**Keywords** binding affinity, epitope processing, vaccine-specific epitope characteristics, escape

**References** Moschella *et al.* 2003

- Two helper T-cell clones specific for this epitope presented in the context of HLA-DR5-11.01 have been characterized. They have different T cell receptor usage. Residue 11 (kdswtvndiqKlvGk) is a natural variant, and K11A, K11G, K11I, and K11L variants were synthesized and studied in two presentation contexts, one as simple peptides, the other embedded in a recombinant protein, GST.
- The two Th clones and the two presentation contexts gave different outcomes with the peptides. K11I was not stimulatory, and was an antagonist in GST, an agonist as a peptide. K11L retained reactivity when presented in the fusion antigen, and had no activity as a peptide. K11G stimulated in both contexts, but the concentrations required for half maximal reactivity were different. K11A could not bind to the MHC in the processed form and could only stimulate when given as a peptide.
- In conclusion, substitutions in epitopes have different effects on Th stimulation depending on the mode of processing, and this should be considered when interpreting Th escape studies and vaccine development.

**HXB2 Location** RT (249–263)

**Author Location** RT (248–262)

**Epitope** KDSWTVNDIQKLVGK

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (DR5-11.01)

**Donor MHC** DR5, DR6

**Assay type** proliferation

**Keywords** binding affinity, epitope processing, vaccine-specific epitope characteristics, escape, TCR usage

**References** Bonomi *et al.* 2000

- Two helper T-cell clones specific for this epitope presented in the context of HLA-DR5-11.01 have been characterized. One of them used TCR V $\beta$ 15, the other used V $\beta$ 2. The substitutions D2A, W4A, D8A, I9A, and K15A were generated and only D8A, I9A failed to react with one clone, while W4A, D8A, I9A were all critical for a reaction with the other clone, showing the TCRs focused on different but overlapping residues.
- Moving the epitope to different contexts in recombinant proteins for presentation by APCs, as well as adding polyanalalanine and polyserine strings to either side of the epitope, influenced reactivity, suggesting processing context can influence the structure of the presentation complex.

**HXB2 Location** RT (249–263)

**Author Location** RT (248–262 HXB2)

**Epitope** KDSSTVNDIQKLVGK

**Subtype** B

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (DRS)

**References** Fenoglio *et al.* 1999

- RT pep23 epitope exhibited antagonistic activity against proliferation of gp120-specific T-cells when flanked by unrelated amino acid sequence.
- The glutathione S-transferase (GST)-peptide system can be used to display peptides; antigenicity was maintained when this peptide was expressed at the C-term end, but antagonism resulted when this peptide was expressed at the N-term end.

**HXB2 Location** RT (249–263)  
**Author Location** (243–263)  
**Epitope** KDSWTVNDIQKLVGK  
**Epitope name** pep23  
**Immunogen** vaccine  
*Vector/Type:* bacteriophage coat protein, di-hydrolipoyl acetyltransferase E2 protein, of *Bacillus stearothermophilus* HIV component: RT  
**Species (MHC)** transgenic mouse (HLA-DR)  
**Assay type** Chromium-release assay  
**Keywords** vaccine antigen design  
**References** De Berardinis *et al.* 2003

- An RT T-helper (KDSWTVNDIQKLVGK) that can be promiscuously presented by multiple HLA-DR molecules, and an RT CTL epitope (ILKEPVHGV) presented by HLA-A2, were displayed using two different antigen presentation systems, bacteriophage virions or E2 protein scaffolds. Both systems enabled display of the epitopes in a mouse model system to the immune system. CTL responses were detected in immunized mice, and were processed correctly for both class I and class II presentation.

**HXB2 Location** RT (249–263)  
**Author Location** RT (IIIB)  
**Epitope** KDSWTVNDIQKLVGK  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming did not induce T-cells that recognize whole protein.

**HXB2 Location** RT (249–263)  
**Author Location** RT (248–262)  
**Epitope** KDSWTVNDIQKLVGK  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** De Berardinis *et al.* 1999

- PBMC from donors GD (HLA DR 11; DRB52) and LD (HLA DR 11, 13; DRB52) recognized this epitope (pep23)
- A subset of T-cell lines generated from these donors were capable of recognizing pep23 expressed on the surface of filamentous phage fd, fused to the major coat protein gVIIIp.
- This peptide was selected to study phage presentation of peptide sequences because it was known to serve as a T-cell helper determinant which could induce proliferation from a naive repertoire Manca *et al.* [1995a]

**HXB2 Location** RT (251–261)  
**Author Location** RT (250–260)  
**Epitope** SSTVNDIQKLV  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (DR5(11.01))  
**References** Manca *et al.* 1996

- This peptide was the minimal stimulatory sequence.
- One Th line was stimulated by p66, one by a Glutathione-S-transferase (GST)-peptide fusion protein.

- Constructs linking GST to the KDSSTVNDIQKLVGK peptide at the N-term end of GST stimulated Th cells, but not constructs linking at the C-term end.
- The C and N termini of GST are not intrinsically permissive or non-permissive, presentation is epitope specific (see FAILKC-NNK for contrast)

**HXB2 Location** RT (258–272)  
**Author Location** RT (IIIB)  
**Epitope** QKLWGKLNWASQIYP  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming did not induce T-cells that recognize whole protein.

**HXB2 Location** RT (271–290)  
**Author Location** RT (271–290 HXB2)  
**Epitope** YPGIKVRQLCKLLRGTKALT  
**Subtype** B  
**Immunogen** HIV-1 infection, in vitro stimulation or selection  
**Species (MHC)** human (DR1, DR2, DR3, DR5, DR7)  
**Keywords** binding affinity, cross-presentation by different HLA  
**References** van der Burg *et al.* 1999

- The goal of this study was to identify Th epitopes that could be cross-presented by multiple class II HLA molecules. 5 RT peptides were identified that could bind to more than one HLA class II protein, but only 2/5 could stimulate strong proliferation responses in PBMC derived from multiple healthy donors.
- This epitope binds with high affinity to HLA-DR1, -DR2, -DR3, -DR5, and -DR7 but not HLA-DR4, and stimulated proliferation in 3/4 individuals with the appropriate HLA alleles.
- This epitope was not able to be naturally processed in protein-pulsed stimulator cells.

**HXB2 Location** RT (271–290)  
**Author Location** RT (271–290 HXB2)  
**Epitope** YPGIKVRQLCKLLRGTKALT  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** van der Burg *et al.* 1999

- Epitope can bind to at least 5 different HLA-DR molecules, and peptide on target cells can elicit Th responses from PBMC cultures from healthy donors, however it does not seem to be processed properly from whole RT or virus.

**HXB2 Location** RT (276–290)  
**Author Location** RT (IIIB)  
**Epitope** WRQLCKLLRGTKALT  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** Manca *et al.* 1995b

- Protein priming induced T-cells that recognize peptide.

**HXB2 Location** RT (285–299)



**Author Location** RT (IIIB)

**Epitope** GTKALTEVIPLTEEA

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Protein priming induced T-cells that recognize peptide.

**HXB2 Location** RT (294–308)

**Author Location** RT (IIIB)

**Epitope** PLTEEALELAENRE

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Protein priming induced T-cells that recognize peptide.

**HXB2 Location** RT (303–317)

**Author Location** RT (IIIB)

**Epitope** LAENREILKEPVHGV

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Protein priming induced T-cells that recognize peptide.

**HXB2 Location** RT (338–352)

**Author Location** RT (338–352 HXB2)

**Epitope** TYQIYQEPFKNLKTG

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DP4)

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, epitope processing, computational epitope prediction, dendritic cells

**References** Cohen *et al.* 2006

- Motif-based quantitative matrices binding predictions, binding assays and cellular assays were used to identify 4 HLA-DP4 epitopes by scanning the whole HIV-1 genome.
- 21 peptides were predicted to bind HLA-DP4, 17 of them did bind in binding assays, 6 of them were good binders. Of the 6 good binders, 4 peptides primed peptide-specific CD4+ T cell lines restricted to HLA-DP4 molecules.
- TYQIYQEPFKNLKTG primed CD4+ T cells that recognized epitopes of the native proteins processed by immature dendritic cells.
- TYQIYQEPFKNLKTG variant had a lower binding capacity to HLA-DP4 molecules, resulting from the unfavorable accommodation of H in the P6 binding pocket.

**HXB2 Location** RT (384–398)

**Author Location** RT (IIIB)

**Epitope** GKTPKFKLPIQKETW

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Protein priming induced T-cells that recognize peptide.

**HXB2 Location** RT (414–428)

**Author Location** Pol (596–610)

**Epitope** WEFVNTPLVKLWYQ

**Epitope name** Pol 596

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Keywords** subtype comparisons

**References** Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds eleven HLA-DR alleles: DRB1\*0101, DRB1\*1501, DRB1\*0401, DRB1\*0405, DRB1\*1101, DRB1\*1302, DRB1\*0701, DRB1\*0802, DRB1\*0901, DRB5\*0101 and DRB4\*0101, with an IC<sub>50</sub> threshold below 1,000 nM.
- This epitope sequence is conserved in 84% of clade B isolates.
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

**HXB2 Location** RT (414–428)

**Author Location** RT (596–610)

**Epitope** WEFVNTPLVKLWYQ

**Epitope name** Pol3

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR(supermotif))

**Country** United Kingdom

**Assay type** Cytokine production, proliferation

**Keywords** supertype, rate of progression

**References** Boaz *et al.* 2003

- Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNP (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naïve).
- Gag-specific CD4+ T cells in LTNP showed increased numbers of IFN  $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.
- Pol3 was 1 of 2 peptides that had a positive correlation between absolute number and percentage of responding cells and viral load. Pol3 responses were also negatively correlated with CD4 counts. In contrast, the absolute number of 3/11 peptides studied were negatively correlated with viral load.

**HXB2 Location** RT (426–448)

**Author Location**

**Epitope** WYQLEKEPIVGAETFYVDGAANR

**Epitope name** HIV-VAX-1050

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 4/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was IVGAET-FYV.

**HXB2 Location** RT (429–443)

**Author Location** RT (IIIB)

**Epitope** LEKEPIVGAETFFYVD

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Protein priming induced T-cells that recognize peptide.

**HXB2 Location** RT (432–450)

**Author Location** RT (431–450 HXB2)

**Epitope** EPIVGAETFYVDGAANRET

**Subtype** B

**Immunogen** HIV-1 infection, in vitro stimulation or selection

**Species (MHC)** human (DR1, DR2, DR3, DR4)

**Keywords** binding affinity, cross-presentation by different HLA

**References** van der Burg *et al.* 1999

- The goal of this study was to identify Th epitopes that could be cross-presented by multiple class II HLA molecules. 5 RT peptides were identified that could bind to more than one HLA class II protein, and but only 2/5 could stimulate strong proliferation responses in PBMC derived from multiple healthy donors.
- This epitope binds with high affinity to HLA-DR1, -DR2, -DR3, and -DR4, but stimulated a strong proliferation response in only 1/4 individuals tested so was not considered broadly cross-presented.

**HXB2 Location** RT (526–540)

**Author Location** RT (526–540 BRU)

**Epitope** IKKEKVYLAWVPAHK

**Epitope name** W9

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide, protein, inactivated HIV *Strain:* B clade BRU *HIV component:* RT, virus *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (Ad, Dd)

**References** Haas *et al.* 1991

- Of 5 mouse inbred lines tested: DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.
- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.
- The peptide KEKVYLAWVPAHKG was one of two RT peptides with Th cells recognition.

**HXB2 Location** RT (528–540)

**Author Location** RT (528–540)

**Epitope** KEKVYLAWVPAHK

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade BRU *HIV component:* RT *Adjuvant:* P3CSS

**Species (MHC)** mouse (H-2b, H-2d, H-2k)

**Assay type** proliferation

**References** Loleit *et al.* 1996

- BALB/c, C3H/Hej, and C57BL/6 mice were immunized with 22-mer lipopeptide tripeptide conjugates P3CSS-[RT-(522-543)] and P3CSS-[RT-(528-549)] of HIV-1 RT, which included the optimal T-helper epitope [RT-(528-540)]. P3CSS conjugated RT epitopes resulted in a specific Th responses, and mice were primed for secondary recognition of native RT. A proximal B cell epitope was also active, containing the motif EQVD.

**HXB2 Location** RT (528–541)

**Author Location** RT (528–543 BRU)

**Epitope** KEKVYLAWVPAHKG

**Epitope name** A3

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide, protein, inactivated HIV *Strain:* B clade BRU *HIV component:* RT, virus *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (Ad, Dd)

**Donor MHC** H-2d, H-2f, H-2k

**References** Haas *et al.* 1991

- Of 5 mouse inbred lines tested: DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.
- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.
- The peptide KEKVYLAWVPAHKG was one of two RT peptides with Th cells recognition. It could by itself prime different strains of mice for RT-specific Th responses, and the C-term half of the peptide is highly conserved in HIV-1, HIV-2 and SIV strains.

**HXB2 Location** RT (528–543)

**Author Location** RT (528–543 BRU)

**Epitope** KEKVYLAWVPAHKGIG

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BRU

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>f</sup>, H-2<sup>k</sup>)

**References** Haas *et al.* 1991

- T-cells from peptide-primed mice could be restimulated by native RT.

**HXB2 Location** RT (529–543)

**Author Location** Pol (711–725)

**Epitope** EKVYLAWVPAHKGIG

**Epitope name** Pol 711

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Keywords** subtype comparisons

**References** Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds ten HLA-DR alleles: DRB1\*0101, DRB1\*1501, DRB1\*0401, DRB1\*0405, DRB1\*1101, DRB1\*0701, DRB1\*0802, DRB1\*0901, DRB5\*0101 and DRB4\*0101, with an IC<sub>50</sub> threshold below 1,000 nM.
- This epitope sequence is conserved in 94% of clade B isolates.
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

**HXB2 Location** RT (529–543)

**Author Location** Protease-RT (711–725)

**Epitope** EKVYLAWVPAHKGIG

**Epitope name** Pol4

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Assay type** proliferation, Intracellular cytokine staining

**Keywords** rate of progression, superinfection

**References** Boaz *et al.* 2003

- Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive).
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN  $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.

**HXB2 Location** RT (529–543)

**Author Location** Pol (711–725)

**Epitope** EKVYLAWVPAHKGIG

**Epitope name** Pol 711

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor, peptide *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (I-Ab and HLA-DR)

**Donor MHC** H-2b

**Keywords** vaccine-specific epitope characteristics, immunodominance

**References** Livingston *et al.* 2002

- 4 Th HIV epitopes presented by HLA-DR molecules were identified that also could be presented by murine class II molecule I-Ab, enabling testing of vaccine strategies in H-2b mice.

- Responses to pooled peptides, polyepitope peptides in a linear construct or in a branched MAP construct, and a DNA polyepitope construct with a CMV promoter were compared. A linear arrangement in polyepitope construct created a junctional epitope that could be disrupted with the addition of GPGPG spacers. The linear polyepitope construct with the GPGPG spacer worked well in terms of eliciting responses to all 4 peptides, using either DNA or protein for the vaccination.
- Although responses to this peptide indicated it was immunodominant, responses to all 4 peptides were made upon vaccination with linear constructs when GPGPG spacers were used.

**HXB2 Location** RT (530–544)

**Author Location** Pol (712–726)

**Epitope** KVYLAWVPAHKGIGG

**Epitope name** Pol 712

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Keywords** subtype comparisons

**References** Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds ten HLA-DR alleles: DRB1\*0101, DRB1\*1501, DRB1\*0401, DRB1\*0405, DRB1\*1101, DRB1\*0701, DRB1\*0802, DRB1\*0901, DRB5\*0101 and DRB4\*0101, with an IC<sub>50</sub> threshold below 1,000 nM.
- This epitope sequence is conserved in 89% of clade B isolates.
- 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

**HXB2 Location** RT (530–544)

**Author Location** RT (712–726)

**Epitope** KVYLAWVPAHKGIGG

**Epitope name** Pol5

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Country** United Kingdom

**Assay type** proliferation, Intracellular cytokine staining

**Keywords** supertype, rate of progression

**References** Boaz *et al.* 2003

- Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive).
- Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN  $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.

- Pol5 was 1 of 2 peptides that had a positive correlation between absolute number and percentage of responding cells and viral load. In contrast, the absolute number of 3/11 peptides studied were negatively correlated with viral load.

### III-B-8 RT-Integrase Helper/CD4+ T-cell epitopes

**HXB2 Location** RT-Integrase (553–3)

**Author Location** RT (720–730 LAI)

**Epitope** SAGIRKVLFLD

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

### III-B-9 Integrase Helper/CD4+ T-cell epitopes

**HXB2 Location** Integrase (16–30)

**Author Location** Pol (758–772)

**Epitope** HSNWRAMASDFNLPP

**Epitope name** Pol 758

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Keywords** subtype comparisons

**References** Wilson *et al.* 2001

- Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.
- This epitope binds eight HLA-DR alleles: DRB4\*0101, DRB5\*0101, DRB1\*0901, DRB1\*0701, DRB1\*1101, DRB1\*0405, DRB1\*0401 and DRB1\*0101, with an IC<sub>50</sub> threshold below 1,000 nM.
- This epitope sequence is conserved in 68% of clade B isolates.
- 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

**HXB2 Location** Integrase (16–30)

**Author Location** Integrase (758–772)

**Epitope** HSNWRAMASDFNLPP

**Epitope name** Pol6

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Country** United Kingdom

**Assay type** proliferation, Intracellular cytokine staining

**Keywords** supertype, rate of progression

**References** Boaz *et al.* 2003

- Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNP (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNP showed increased numbers of IFN  $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.
- Pol6 was 1 of 3 peptides that had a negative correlation between absolute number of responding cells and viral load.

**HXB2 Location** Integrase (70–84)

**Author Location** Integrase (70–84 clade B consensus)

**Epitope** GKILVAVHVASGYI

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1302, DRB1\*1501, DRB5\*0101)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was GKILVAVHVASGYI, shorter IILVAVHVASG peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** Integrase (94–116)

**Author Location**

**Epitope** GQETAYFILKLAGRWPVKVIHTD

**Epitope name** HIV-VAX-1047

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 2/13 US test subjects responded to this 23-mer by CD4 Elispot assay. The core computer-predicted peptide was ILKLAGRWP.

**HXB2 Location** Integrase (172–186)  
**Author Location** RT (899–913 LAI)  
**Epitope** LKTAVQMAVFIHNFK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Schrier *et al.* 1989  
 • Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** Integrase (173–187)  
**Author Location** Pol (915–929)  
**Epitope** KTAVQMAVFFIHNFKR  
**Epitope name** Pol 915  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR supermotif)  
**Keywords** subtype comparisons  
**References** Wilson *et al.* 2001  
 • Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.  
 • This epitope binds seven HLA-DR alleles: DRB5\*0101, DRB1\*1302, DRB1\*1101, DRB1\*0405, DRB1\*0401, DRB1\*1501 and DRB1\*0101, with an IC<sub>50</sub> threshold below 1,000 nM.  
 • This epitope sequence is conserved in 94% of clade B isolates.  
 • 6/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

**HXB2 Location** Integrase (173–187)  
**Author Location** Integrase (915–929)  
**Epitope** KTAVQMAVFIHNFKR  
**Epitope name** Pol7  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR supermotif)  
**Country** United Kingdom  
**Assay type** proliferation, intracellular cytokine staining  
**Keywords** supertype, rate of progression, immunoprophylaxis  
**References** Boaz *et al.* 2003  
 • Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNPs (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.  
 • Gag-specific CD4+ T cells in LTNPs showed increased numbers of IFN  $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.

**HXB2 Location** Integrase (187–204)  
**Author Location** (clade B consensus)  
**Epitope** RKGIGGYSAGERIVDII

**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*0101, A\*0201, B\*4001, C\*0304, DRB1\*0801, DRB1\*1301  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** escape  
**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- RKGIGGYSAGERIVDII variant coincided with a positive response. RKGIGGYSAGkRIVDII variant 4 weeks later coincided with no response.

**HXB2 Location** Integrase (195–211)  
**Author Location** (clade B consensus)  
**Epitope** SAGERIVDIIATDIQTK  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*0101, A\*0201, B\*4001, C\*0304, DRB1\*0801, DRB1\*1301  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** escape  
**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- SAGERIVDIIATDIQTK variant coincided with a positive response. SAGkRIVDIIATDIQTKI variant 4 weeks later coincided with a diminished response.

**HXB2 Location** Integrase (196–210)  
**Author Location** RT (923–937 LAI)  
**Epitope** AGERIVDIIATDIQT  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Schrier *et al.* 1989  
 • Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** Integrase (214–228)  
**Author Location** Pol (956–970)  
**Epitope** QKQITKIQNFVYYR  
**Epitope name** Pol 956  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR supermotif)  
**Keywords** subtype comparisons  
**References** Wilson *et al.* 2001  
 • Eleven peptides were identified that had the HLA-DR supermotif, all were found to bind to MHC class II DR molecules and all elicited proliferative responses from multiple HIV-infected donors.

- This epitope binds twelve HLA-DR alleles: DRB4\*0101, DRB5\*0101, DRB1\*0901, DRB1\*0802, DRB1\*0701, DRB1\*1302, DRB1\*1201, DRB1\*1101, DRB1\*0405, DRB1\*0401, DRB1\*1501 and DRB1\*0101, with an IC<sub>50</sub> threshold below 1,000 nM.
- This epitope sequence is conserved in 95% of clade B isolates.
- 8/22 HIV infected individuals responded to this epitope (13/22 responded to some of the DR supermotif epitopes, the 9 non-responder peptides tended to also not have recall responses to rec HIV-1 whole proteins)

**HXB2 Location** Integrase (214–228)

**Author Location** Integrase (956–970)

**Epitope** QKQITKIQNFRVYYR

**Epitope name** Pol8

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR supermotif)

**Country** United Kingdom

**Assay type** proliferation, Intracellular cytokine staining

**Keywords** supertype, rate of progression

**References** Boaz *et al.* 2003

- Proliferative and cytokine (IFN $\gamma$  and IL-2) immune responses to 11 previously defined (Wilson 2001), and immunodominant and broadly cross-reactive Th epitopes and to p24 overlapping peptides were characterized in 10 LTNP (chronically infected, asymptomatic, long term non-progressors, CD4+ T cells >500 after 15 years) and 7 SPs (slow progressors, CD4+ T cell declined to <500 after 15 years. Patients were treatment-naive.
- Gag-specific CD4+ T cells in LTNP showed increased numbers of IFN  $\gamma$  and IL-2 producing cells compared to SPs. Cytokine production and proliferative responses were negatively correlated with the viral load and positively correlated with the CD4+ T cell count. IL-2, but not IFN $\gamma$ , levels were correlated with proliferation.
- Pol8 was the only peptide that had higher cytokine responses in LTNP than SPs ( $p = 0.0431$ ). No peptide had detectable differences in proliferative responses between the two groups.

**HXB2 Location** Integrase (215–227)

**Author Location** RT (942–954 LAI)

**Epitope** KQITKIQNFRVYY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** Integrase (242–259)

**Author Location** (clade B consensus)

**Epitope** LWKGEGAVVIQDNSDIKV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0101, A\*0201, B\*4001, C\*0304, DRB1\*0801, DRB1\*1301

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- LWKGEGAVVIQDNSDIKV variant coincided with a positive response. LWKGEGAVVIQDNSDIKV variant 4 weeks later coincided with a diminished response.

**HXB2 Location** Integrase (242–264)

**Author Location**

**Epitope** LWKGEGAWIQDNSDIKWPRRK

**Epitope name** HIV-VAX-1049

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 1/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was WIQDNSDI.

**HXB2 Location** Integrase (250–267)

**Author Location** Integrase (250–267 B Consensus)

**Epitope** VIQDNSDIKVVPRRKAKI

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP responded to many peptides, comparable to acute STI.

**HXB2 Location** Integrase (250–267)

**Author Location** Integrase (250–267)

**Epitope** VIQDNSDIKVVPRRKAKI

**Subtype** B

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Netherlands  
**Assay type** Cytokine production  
**References** Geels *et al.* 2006
- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
  - Autologous sequences corresponding to known and predicted Th epitopes were analyzed. VIQDNSDIKVVPRRKAKI had fixation of 1 mutation (VIQDNSDIK[v/a]VPRRKAKI) in 1 of the patients.
- HXB2 Location** Integrase (250–267)  
**Author Location** (clade B consensus)  
**Epitope** VIQDNSDIKVVPRRKAKI  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*0101, A\*0201, B\*4001, C\*0304, DRB1\*0801, DRB1\*1301  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** escape  
**References** Rychert *et al.* 2007
- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
  - VIQDNSDIKVVPRRKAKI variant coincided with a positive response. VIQDNSDIKVVPRRKAKI variant 4 weeks later also coincided with a positive (but increased) response.

### III-B-10 Pol Helper/CD4+ T-cell epitopes

- HXB2 Location** Pol  
**Author Location** RT (248–256 HXB2)  
**Epitope**  
**Subtype** B  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (DR5)  
**References** Manca *et al.* 1995b
- CD4+ T-cell lines from uninfected individuals by stimulation with p66-pulsed APC.
  - TcR V $\beta$  D $\beta$  J $\beta$  sequences were obtained from p66-specific T-cell clones.
  - There were multiple responses to peptides throughout p66, but because of uncertain locations, they have not been mapped.
  - Response to peptide 248-256 was associated with DR5.
- HXB2 Location** Pol  
**Author Location** RT  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Env, Gag, Pol *Adjuvant:* IFN $\gamma$ , IL-2, IL-4

- Species (MHC)** mouse (H-2<sup>d</sup>)  
**Keywords** Th1  
**References** Kim *et al.* 2000
- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of Th1 cytokine IFN- $\gamma$  drove Th1 immune responses and enhanced CTL responses.
- HXB2 Location** Pol  
**Author Location** RT  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* Salmonella *HIV component:* RT  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**References** Burnett *et al.* 2000
- A live attenuated bacterial vaccine, Salmonella SL3261-pHART, with an inserted HIV RT gene in the Lpp-OmpA-HIV fusion protein, induced a lymphoproliferative Th response in BALB/c mice.
- HXB2 Location** Pol  
**Author Location** Gag/Pol  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Gag, Pol, Vif *Adjuvant:* B7, IL-12  
**Species (MHC)** mouse  
**References** Kim *et al.* 1997b
- A gag/pol DNA vaccine delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12 gives a dramatic increase in both the cytotoxic and proliferative responses in mice.
- HXB2 Location** Pol  
**Author Location** Gag/Pol  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Gag, gp160, Pol *Adjuvant:* CD86  
**Species (MHC)** mouse  
**References** Kim *et al.* 1997d
- A gag/pol DNA vaccine delivered in conjunction with the plasmid encoding the co-stimulatory molecule CD86 gives an increase in proliferative responses to Pr55 in mice.
- HXB2 Location** Pol  
**Author Location** Gag/Pol (MN)  
**Epitope**  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade MN *HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86  
**Species (MHC)** chimpanzee  
**References** Kim *et al.* 1998
- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

**HXB2 Location** Pol**Author Location** Pol**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Blankson *et al.* 2001

- 5/10 chronically HIV infected patients with low CD4+ counts who received HAART therapy and experienced immune reconstitution displayed p24, p17 and p66 T-helper CD4 proliferative responses, in contrast to 0/8 chronically HIV infected patients with high CD4+ counts at the initiation of antiretroviral treatment.
- This surprising result could be due to the low CD4 nadir patients being more likely to have thymic regeneration or a peripheral expansion of T cells.

**HXB2 Location** Pol**Author Location** p66**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.

**HXB2 Location** Pol**Author Location** p66**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Palmer *et al.* 2002

- CD4+ T cell proliferative responses from 33 HIV-1 infected patients with HAART suppression were compared to 19 patients with active viral replication (HAART failures and HAART naive). Patients with HAART suppression showed stronger p24- and p66-specific proliferative responses compared to patient groups with active HIV-1 replication, suggesting active viral replication *in vivo* specifically reduces proliferation responses.
- No differences in the frequency of HIV-specific CD4+ T-cells that were positive for cytokine secretion in a flow cytometry assay were found in the HAART suppressed group versus the group with active viral replication.

**HXB2 Location** Pol**Author Location** (BRU)**Epitope****Subtype** B**Immunogen** vaccine**Vector/Type:** inactivated HIV **Strain:** B**clade** BRU **HIV component:** RT, virus**Adjuvant:** Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse**References** Haas *et al.* 1991

- Of 5 mouse inbred lines tested DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.
- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.

### III-B-11 Vif Helper/CD4+ T-cell epitopes

**HXB2 Location** Vif (4–26)**Author Location****Epitope** RWQVMIVWQVDRMRIRTWNSLVK**Epitope name** HIV-VAX-1052**Immunogen** HIV-1 infection**Species (MHC)** human (DRB\*0101)**Country** United States**Assay type** CD4 T-cell Elispot - IFN $\gamma$ **Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 4/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was WQVDRM-RIR.

**HXB2 Location** Vif (65–76)**Author Location** Vif (65–80)**Epitope** VITTYWGLHTGE**Immunogen** HIV-1 infection**Species (MHC)** human**References** Ranki *et al.* 1997

- T-cell response to this epitope persisted after seroreversion.

**HXB2 Location** Vif (81–96)**Author Location** Vif (81–96)**Epitope** LGQGVSI EWKQRYST**Immunogen** HIV-1 infection**Species (MHC)** human**References** Ranki *et al.* 1997

- T-cell response to this epitope persisted after seroreversion.

**HXB2 Location** Vif (144–158)**Author Location** Vif (144–158 clade B consensus)**Epitope** SLQYLALVALVAPKK**Subtype** B**Immunogen** HIV-1 infection, computer prediction**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1501, DRB5\*0101)



**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was SLQYLALVALVAPKK, shorter LQYLALVALVAPKK peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** Vif

**Author Location** Vif

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Nef, Vif, Vpu

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** subtype comparisons, Th1

**References** Ayyavoo *et al.* 2000

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN- $\gamma$  levels.
- Antigen stimulation increased IFN- $\gamma$  production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

### III-B-12 Vpr Helper/CD4+ T-cell epitopes

**HXB2 Location** Vpr (58–72)

**Author Location** Vpr (58–72 clade B consensus)

**Epitope** EAIRILQQLLFIHF

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB1\*0101, DRB1\*0405, DRB1\*1501)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR

binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.

- While the reacting peptide was EAIRILQQLLFIHF, shorter IRILQQLLF peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** Vpr (60–82)

**Author Location**

**Epitope** IIRILQQLLFIHFIRIGCQHSRIG

**Epitope name** HIV-VAX-1053

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 2/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was LLFIHFIRIG.

**HXB2 Location** Vpr (65–82)

**Author Location** Vpr (65–82 clade B consensus)

**Epitope** QQLLFIHFIRIGCRHSRIG

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB1\*0101, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1302, DRB1\*1501, DRB5\*0101)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was QQLLFIHFIRIGCRHSRIG, shorter LFIHFIRIGCRHSR peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** Vpr (66–80)

**Author Location** Vpr (66–80 IIIB)

**Epitope** QLLFIHFIRIGCRHSR

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Sarobe *et al.* 1994

- Included as a Th stimulatory component of peptide vaccines that also incorporated B-cell epitopes.

**HXB2 Location** Vpr (66–80)

**Author Location** Vpr (66–80 IIIB)

**Epitope** QLLFIHFRIGCRHSR

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Sarobe *et al.* 1994

- This peptide was found to stimulate proliferative responses in 37.5% of HIV-1 positive individuals.

### III-B-13 Tat Helper/CD4+ T-cell epitopes

**HXB2 Location** Tat (1–20)

**Author Location** Tat (1–20 LAI)

**Epitope** MEPVDPRLEPWKHPGSQPKT

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Tat (16–35)

**Author Location** Tat (16–35 LAI)

**Epitope** SQPKTACTTCYCKKCCFHCQ

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Tat (17–32)

**Author Location** Tat (17–32 HXB2)

**Epitope** QPKTACTNCYCKKCCF

**Epitope name** D26

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR5? plus others)

**Keywords** immunodominance

**References** Blazevic *et al.* 1993

- 9/14 (64%) of HIV-1 positive patients had proliferative T-cell responses associated with IL-2 production against at least one Tat-derived synthetic peptides of twelve overlapping 15-16 mer peptides spanning Tat. T cell proliferation was associated with IL-2 production.
- 3/12 peptides were recognized.

- This immunodominant, highly conserved and most frequently recognized peptide was recognized by 57% of the HIV-1 infected patients. A beta-sheet secondary structure was predicted at aa residues 21–28, but no amphipathic helix structure, suggested to be most favorable for T-cell epitopes, was indicated.

- This peptide contained epitopes restricted by several HLA DR alleles, although the frequency of DR5 was enriched (3/6) among the patients that recognized the peptide.

**HXB2 Location** Tat (17–32)

**Author Location** Tat (17–32)

**Epitope** QPKTACTNCYCKRCCF

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Ranki *et al.* 1997

- T-cell response to this epitope persisted after seroreversion.

**HXB2 Location** Tat (25–47)

**Author Location**

**Epitope** CYCKHCSYHCLVCFQTKGLGISY

**Epitope name** HIV-VAX-1054

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 3/13 US test subjects responded to this 23-mer by CD4 Elispot assay. The core computer-predicted peptide was YH-CLVCFQT.

**HXB2 Location** Tat (31–50)

**Author Location** Tat (31–50 LAI)

**Epitope** CFHCQVCFTTKALGISYGRK

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Tat (33–48)

**Author Location** Tat (33–48 HXB2)

**Epitope** HCQVCFITKALGISYG

**Epitope name** D28

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR5? plus others)

**References** Blazevic *et al.* 1993

- 9/14 (64%) of HIV-1 positive patients had proliferative T-cell responses associated with IL-2 production against at least one Tat-derived synthetic peptides of twelve overlapping 15-16 mer peptides spanning Tat. T cell proliferation was associated with IL-2 production.
- 3/12 peptides were recognized.
- 4/14 HIV+ people recognized this peptide.
- An alpha-helix structure was predicted at residues 39-44, but charge patterns did not indicate it was an amphipathic helix, suggested to be most favorable for T-cell epitopes.
- This peptide contained epitopes restricted by several HLA DR alleles, although the frequency of DR5 was enriched (2/4) among the patients that recognized the peptide.

**HXB2 Location** Tat (33–48)

**Author Location** Tat (33–48)

**Epitope** HCQVCFMTKGLGISYG

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Ranki *et al.* 1997

- T-cell response to this epitope persisted after seroreversion.

**HXB2 Location** Tat (36–50)

**Author Location** Tat (36–50 HTLV IIIB)

**Epitope** VCFITKALGISYGRK?

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

*HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide-2 (MALP-2)

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Assay type** Cytokine production, proliferation, T-cell Elispot, Th support of CTL response

**Keywords** Th1, Th2, mucosal immunity

**References** Borsutzky *et al.* 2003

- BALB/c mice that were vaccinated intranasally with Tat protein plus mucosal adjuvant macrophage-activating lipopeptide-2 (MALP-2) had increased proliferative, antibody, and IFN- $\gamma$  producing T-cell responses than did with Tat+IFA delivered by the i.p. route.
- IFA as adjuvant stimulated a Th2-dominant response pattern, and MALP-2 as adjuvant shifted to a Th1 response. Anti-Tat IgG1 dominated the Ab response with IFA, IgG2b dominated with MALP-2. In animals vaccinated with Tat+MALP-2, IFN- $\gamma$  and IL-2 were the most prominent cytokines, with some IL-6. In contrast, in mice vaccinated with Tat+IFA, IL-6 was the dominant cytokine. Secreted IL-4, IL-5 and IL-10 were below the detection limit in both cases.
- The strongest proliferation of spenocytes was observed was after re-stimulation with residues 36-50 and 56-70.

**HXB2 Location** Tat (41–50)

**Author Location** Tat (40–50 C consensus)

**Epitope** KGLGISYGRK?

**Subtype** C

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* C clade consensus

*HIV component:* Tat *Adjuvant:* ubiquitin

**Species (MHC)** mouse

**Donor MHC** H-2d

**Assay type** proliferation, CD4 T-cell Elispot - IFN $\gamma$

**Keywords** Th1, vaccine antigen design

**References** Ramakrishna *et al.* 2004

- BALB/c and C57BL/6 mice were intramuscularly immunized with a codon optimized HIV-1 C-consensus Tat DNA vaccine that was linked to ubiquitin to facilitate rapid processing. Ubiquitin and codon optimization enhanced Th1 T cell responses, with increased proliferative responses, cytotoxic responses, and Th1 responses measured by IFN $\gamma$  EliSpot, but not the Th2 responses, measured by IL-4 EliSpot.
- Several immunogenic regions in HIV-1 Tat were identified in BALB/c mice using EliSpot. The strongest immune response was within the core region of Tat; the peptides based on the C subtype consensus positions 30-50 and 40-60 gave the strongest EliSpot responses in BALB/c mice, suggesting a putative helper T-cell epitope spanning the region of overlap, residues 40-50.

**HXB2 Location** Tat (46–65)

**Author Location** Tat (46–65 LAI)

**Epitope** SYGRKKRRQRRPPQGSQTH

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Tat (56–70)

**Author Location** Tat (56–70 HTLV IIIB)

**Epitope** RRAHQNSQTHQASLS?

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

*HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide-2 (MALP-2)

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Assay type** Cytokine production, proliferation, T-cell Elispot, Th support of CTL response

**Keywords** Th1, Th2

**References** Borsutzky *et al.* 2003

- BALB/c mice that were vaccinated intranasally with Tat protein plus mucosal adjuvant macrophage-activating lipopeptide-2 (MALP-2) had increased proliferative, antibody, and IFN- $\gamma$  producing T-cell responses than did with Tat+IFA delivered by the i.p. route.
- IFA as adjuvant stimulated a Th2-dominant response pattern, and MALP-2 as adjuvant shifted to a Th1 response. Anti-Tat IgG1 dominated the Ab response with IFA, IgG2b dominated with MALP-2. In animals vaccinated with Tat+MALP-2, IFN- $\gamma$  and IL-2 were the most prominent cytokines, with some IL-6. In contrast, in mice vaccinated with Tat+IFA, IL-6 was the

dominant cytokine. Secreted IL-4, IL-5 and IL-10 were below the detection limit in both cases.

- The strongest proliferation of spenocytes was observed was after re-stimulation with residues 36-50 and 56-70.

**HXB2 Location** Tat (61–80)

**Author Location** Tat (61–80 LAI)

**Epitope** GSQTHQVLSLSKQPTSQPRGD

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally; rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Tat (65–80)

**Author Location** Tat (65–80 HXB2)

**Epitope** HQASLSKQPTSQPRGD

**Epitope name** D32

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR2? plus others)

**References** Blazevic *et al.* 1993

- 9/14 (64%) of HIV-1 positive patients had proliferative T-cell responses associated with IL-2 production against at least one Tat-derived synthetic peptides of twelve overlapping 15-16 mer peptides spanning Tat. T cell proliferation was associated with IL-2 production.
- 3/12 Tat peptides were recognized.
- 3/14 HIV+ people recognized this peptide.
- An alpha-helix structure was predicted at residues 65-72, but charge patterns did not indicate it was an amphipathic helix, suggested to be most favorable for T-cell epitopes..
- This peptide contained epitopes restricted by several HLA DR alleles, although the frequency of DR2 was enriched (2/3) among the patients that recognized the peptide.

**HXB2 Location** Tat (67–86)

**Author Location** Tat (67–86 LAI)

**Epitope** VSLSKQPTSQPRGDPTGPKE

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Tat

**Author Location** Tat

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA, DNA with protein boost

*Strain:* B clade LAI *HIV component:* Gag,

Nef, Tat *Adjuvant:* IL-18

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** Th1, Th2

**References** Billaut-Mulot *et al.* 2001

- DNA vaccinated BALB/c mice primed and boosted with a multiepitopic vaccine with IL18 gave lymphoproliferative responses 7 weeks post immunization.
- Strong but non-lasting HIV-specific CTL responses were detected by a Cr-release assay and DNA prime + DNA boost was more effective than DNA prime + protein boost.
- Immunization with either the multiepitopic DNA or with the mixed DNA vaccine resulted in Th1 cytokines production (IL-2 and IFN- $\gamma$ ) in spleen cell cultures stimulated by Tat and Gag, while Th2 cytokines IL-4 and IL-10 production was not detectable.
- Co-administration of IL18 increased T-cell responses but decreased anti-HIV antibody levels.

**HXB2 Location** Tat

**Author Location** Tat

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Nef,

Rev, Tat

**Species (MHC)** human

**Keywords** HAART, ART

**References** Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN- $\gamma$  production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

**HXB2 Location** Tat

**Author Location** Tat

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA *HIV component:* Nef,

Rev, Tat *Adjuvant:* CpG immunostimulatory

sequence (ISS)

**Species (MHC)** human

**Keywords** review, Th1

**References** Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on CpG induction of Th1 cytokines and enhanced immune responses, and HIV-1 DNA vaccine boosting of CTL and Th proliferative responses in asymptomatic HIV+ individuals.

**HXB2 Location** Tat

**Author Location** Tat

**Epitope****Immunogen** in vitro stimulation or selection**Species (MHC)** human**Keywords** dendritic cells, Th1, Th2**References** Corinti *et al.* 2002

- In vitro delivery of recombinant Tat protein conjugated to red blood cells (RBCs) via avidin-biotin bridges (RBC-Tat) to human dendritic cells was compared to dendritic cells pulsed with rec Tat.
- Dendritic cells pulsed with RBC-Tat elicited specific and significantly stronger CD4+ and CD8+ T-cell responses and required 1250-fold less antigen than DCs stimulated with soluble Tat.
- Dendritic cells which were matured in the presence of IFN $\gamma$  induced elevated IL-12 and TNF- $\alpha$  secretion. IFN $\gamma$  upregulated IP-10 and down regulated TARC, chemokines which attract Th1 and Th2 cells, respectively.

**HXB2 Location** Tat**Author Location** Tat (IIIB, BH10)**Epitope****Subtype** B**Immunogen** in vitro stimulation or selection**Species (MHC)** human**Keywords** epitope processing, vaccine-specific epitope characteristics, dendritic cells, Th1**References** Fanales-Belasio *et al.* 2002b

- Biologically active HIV-1 Tat is readily taken up by monocyte-derived dendritic cells (MDDC) (and activated endothelial cells), but not other APCs. Tat must be in a native, non-oxidized conformation for efficient uptake. Tat upregulates MHC molecules, IL-12, TNF $\alpha$ , RANTES and MIP-1- $\alpha$  and MIP-1- $\beta$  production which drives Th1 immune responses and enhances antigen presentation.
- Native Tat enhanced the antigen presentation of MDDC and boosted proliferative recall and allogeneic antigen responses, and the authors propose it could be used as an adjuvant to drive the immune response as well as an antigen.

**HXB2 Location** Tat**Author Location** Tat**Epitope****Immunogen** vaccine*Vector/Type:* DNA, protein *HIV component:* Tat *Adjuvant:* aluminum hydroxide, Ribi adjuvant (MPL+TDM) (RIBI)**Species (MHC)** macaque**Assay type** Cytokine production, Delayed-type hypersensitivity (DTH)**Keywords** review, early-expressed proteins, Th1**References** Fanales-Belasio *et al.* 2002a

- HIV-1 Tat protein has several virtues vaccine component. It is an early expressed protein, and though variable, contains conserved T-cell and B-cell epitopes that allow cross-clade recognition. It is efficiently taken up by monocyte-derived dendritic cells (MDDCs) and in this context can stimulate Th1 immune responses. A Tat based vaccine can elicit an immune response that can control primary infection in monkeys that are in early stage of infection with SHIV89.6P.

**HXB2 Location** Tat**Author Location** Tat (1-72)**Epitope****Subtype** B**Immunogen** vaccine*Vector/Type:* protein, nanoparticle *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* aluminum hydroxide, lipid A**Species (MHC)** mouse**Donor MHC** H-2d**Assay type** Cytokine production, proliferation**Keywords** Th1, Th2, adjuvant comparison, vaccine antigen design**References** Cui *et al.* 2004

- Mice were subcutaneously injected on day 0 and 14 with either Alum and Tat (Th2 control) or Lipid A-adjuvanted Tat (Th1 control), or Tat coated anionic nanoparticles. Analysis of Ab and cytokine release in splenocytes (day 28) showed both IgG and IgM Ab responses; immunization with Tat-coated nanoparticles induced a Th1-biased immune response.
- IFN  $\gamma$  responses were 3.3-fold stronger with Tat and either Lipid-A or coated nanoparticles than with Tat and Alum.

**III-B-14 Rev Helper/CD4+ T-cell epitopes****HXB2 Location** Rev (9-23)**Author Location** Rev (9-23 HXB2)**Epitope** DEELIRTVRLIKLLY**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Blazevic *et al.* 1995

- One of four peptides that stimulates in PBLs from HIV-1 + donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide were stimulated.

**HXB2 Location** Rev (11-27)**Author Location** Rev (11-276 clade B consensus)**Epitope** ELLKTVRLIKFLYQSNP**Subtype** B**Immunogen** HIV-1 infection, computer prediction**Species (MHC)** human (DRB1\*0101, DRB1\*0301, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1302, DRB1\*1501)**Country** Brazil**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.

- While the reacting peptide was ELLKTVRLIKFLYQSNP, shorter LLKTVRLIKFLYQ peptide was predicted by TEPI-TOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** Rev (14–30)  
**Author Location** Rev (14–30 B Consensus)  
**Epitope** KTVRLIKFLYQSNPPPS  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding  
**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection  
**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** Rev (16–35)  
**Author Location** Rev (16–35 LAI)  
**Epitope** VRLIKFLYQSNPPNPEGTR  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade LAI  
*HIV component:* Nef, Rev, Tat  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Rev (25–39)  
**Author Location** Rev (25–39 HXB2)  
**Epitope** SNPPNPEGTRQARR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Blazevic *et al.* 1995

- One of four peptides that stimulates in PBLs from HIV-1 + donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide were stimulated.

**HXB2 Location** Rev (31–50)  
**Author Location** Rev (31–50 LAI)  
**Epitope** PEGTRQARRNRRRRWRERQR  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade LAI  
*HIV component:* Nef, Rev, Tat  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Rev (33–48)  
**Author Location** Rev (33–48 HXB2)  
**Epitope** GTRQARRNRRRRWRER  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Blazevic *et al.* 1995

- One of four peptides that stimulates in PBLs from HIV-1 + donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide were stimulated.

**HXB2 Location** Rev (41–56)  
**Author Location** Rev (41–56 HXB2)  
**Epitope** RRRRWRETRQRIHSIS  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Blazevic *et al.* 1995

- One of four peptides that stimulates in PBLs from HIV-1 + donors both CD4+ Th cell proliferation and CTL to autologous targets incubated with peptide were stimulated.

**HXB2 Location** Rev (76–95)  
**Author Location** Rev (76–95 LAI)  
**Epitope** PPLERLTLDCNEDCGTSGTQ  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade LAI  
*HIV component:* Nef, Rev, Tat  
**Species (MHC)** mouse (H-2<sup>b</sup>)  
**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Rev (96–116)  
**Author Location** Rev (96–116 LAI)  
**Epitope** GVGSPQILVESPTVLESGTKE  
**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI  
*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Rev**Author Location** Rev**Epitope****Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Rev

**Species (MHC)** mouse**Keywords** HAART, ART**References** Chan *et al.* 1998

- Rev M10 is a construct that was introduced into mice through a genetic vaccination.
- Rev was used to test for down-regulation of HIV-1 in infected cells as a method for gene therapy – in the course of this study, Rev-specific IL-2 producing Th cells developed in the mice.

**HXB2 Location** Rev**Author Location** Rev**Epitope****Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Nef, Rev, Tat

**Species (MHC)** human**Keywords** HAART, ART**References** Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN- $\gamma$  production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

**HXB2 Location** Rev**Author Location** Rev**Epitope****Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)

**Species (MHC)** human**Keywords** review, Th1**References** Calarota & Wharen 2001

- This review discusses the cellular immune response, and comments on CpG induction of Th1 cytokines and enhanced immune responses, and HIV-1 DNA vaccine boosting of CTL and Th proliferative responses in asymptomatic HIV+ individuals.

**HXB2 Location** Rev**Author Location** Rev**Epitope****Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor  
*Strain:* B clade MN *HIV component:* Env, Rev *Adjuvant:* Bupivacaine

**Species (MHC)** human**Keywords** early-expressed proteins**References** MacGregor *et al.* 2002

- A phase I clinical trial of a HIV-1 Env and Rev DNA vaccine with a CMV promoter was conducted and Th proliferative, CTL and Elispot responses monitored. The construct was modified for safety and included no LTRs or packaging signals. The vaccine strategy was safe, and elicited strong CD4+ T cell responses, but not CD8 T-cell responses. Rev elicited strong Th responses, and is a early produced protein so may confer advantages.
- With a 300 ug dose, 4/6 individuals had a lymphocyte proliferation (LP) responses to gp120, 3/6 to Rev.
- With a 1000 ug dose, 4/6 individuals had a LP and 2/6 had IFN $\gamma$  Elispot responses to gp160; 3/6 had LP, and 4/6 had IFN $\gamma$  Elispot responses to Rev.
- No responses to three specific CTL epitopes were observed by Elispot in individuals with appropriate HLA. Some cytotoxic activity against whole protein was observed that was CD4+ T-cell mediated.

**III-B-15 Vpu Helper/CD4+ T-cell epitopes****HXB2 Location** Vpu (6–20)**Author Location** Vpu (6–20 clade B consensus)**Epitope** VLAIVALVVATIIAI**Subtype** B**Immunogen** HIV-1 infection, computer prediction**Species (MHC)** human**Country** Brazil**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.

**HXB2 Location** Vpu (19–34)**Author Location** Vpu (19–34)**Epitope** AIVVWSIVLIEYRKIL**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Ranki *et al.* 1997

- T-cell response to this epitope persisted after seroreversion.

**HXB2 Location** Vpu (20–41)

**Author Location**

**Epitope** AIWWSIVFIEYRKILRQRKIDR

**Epitope name** HIV-VAX-1056

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 1/13 US test subjects responded to this 23-mer by CD4 EliSpot assay. The core computer-predicted peptide was VFIEYRKIL.

**HXB2 Location** Vpu

**Author Location** Vpu

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Nef, Vif, Vpu

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** subtype comparisons, Th1

**References** Ayyavoo *et al.* 2000

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN- $\gamma$  levels.
- Antigen stimulation increased IFN- $\gamma$  production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.
- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

### III-B-16 gp160 Helper/CD4+ T-cell epitopes

**HXB2 Location** gp160 (19–31)

**Author Location** gp160 (19–31 clade B consensus)

**Epitope** TMLLGMLMICSAA

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB1\*0101, DRB1\*0405, DRB1\*1101)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was TMLLGMLMICSAA, shorter MLLGMLMICSAA peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** gp160 (30–51)

**Author Location** gp120 (30–51 IIIB)

**Epitope** ATEKLWTVYYGVVPVWKEATTT?

**Epitope name** A1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, mean SI = 4.6.

**HXB2 Location** gp160 (31–45)

**Author Location** Env (31–45 HXB2)

**Epitope** TEKLWTVYYGVVPVW

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DP4)

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, epitope processing, computational epitope prediction, dendritic cells

**References** Cohen *et al.* 2006

- Motif-based quantitative matrices binding predictions, binding assays and cellular assays were used to identify 4 HLA-DP4 epitopes by scanning the whole HIV-1 genome.
- 21 peptides were predicted to bind HLA-DP4, 17 of them did bind in binding assays, 6 of them were good binders. Of the 6 good binders, 4 peptides primed peptide-specific CD4+ T cell lines restricted to HLA-DP4 molecules.

**HXB2 Location** gp160 (32–44)

**Author Location** gp120 (39–51)

**Epitope** EQLWTVYYGVVPV

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse (H-2<sup>bxk</sup>)

**References** Sastry & Arlinghaus 1991



- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

**HXB2 Location** gp160 (38–48)

**Author Location** gp120 (45–55)

**Epitope** VYYGVPVWKEA

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse (H-2<sup>b<sup>bk</sup></sup>, H-2<sup>s<sup>sd</sup></sup>)

**References** Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

**HXB2 Location** gp160 (38–48)

**Author Location** Env (45–55)

**Epitope** VYYGVPVWKEA

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** macaque

**References** Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys.

**HXB2 Location** gp160 (38–48)

**Author Location** Env (45–55)

**Epitope** VYYGVPVWKEA

**Immunogen** HIV-1 infection

**Species (MHC)** human, chimpanzee

**References** Nehete *et al.* 1998b

- Seven out of nine HIV-infected chimpanzees and eight out of seventeen HIV-positive humans exhibited positive proliferative responses to this conserved peptide (peptide 104) – no HIV negative individuals showed a response.
- This peptide, along with 4 other peptides from conserved regions of envelope, can induce proliferative responses to HIV and may be useful for vaccines.
- Peptide 104 elicited proliferative responses in inbred mouse strains and outbred rhesus monkeys in previous study by same group.

**HXB2 Location** gp160 (41–54)

**Author Location** gp120 (48–61)

**Epitope** GVPVWKEATTLFC

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse (H-2<sup>s<sup>sd</sup></sup>)

**References** Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

**HXB2 Location** gp160 (41–54)

**Author Location** Env (48–60)

**Epitope** GVPVWKEATTLFC

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** macaque

**References** Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Despite the proliferative response to this peptide in mice, no response was observed in 3 rhesus monkeys.

**HXB2 Location** gp160 (41–60)

**Author Location** gp120 (40–59 89.6)

**Epitope** GVPVWREATTLFCASDAKA

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6

*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** immunodominance

**References** Dai *et al.* 2001

- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2<sup>k</sup> and BALB/c H-2<sup>d</sup> mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
- This peptide was recognized by 10/10 BALB/c with an average SI of 6.4, the strongest reaction among BALB/c mice, but not by CBA/J mice, but recognized well not by CBA/J mice, so is considered to be uniquely immunodominant for H-2<sup>d</sup>
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

**HXB2 Location** gp160 (41–60)

**Author Location** gp120 (40–59 89.6)

**Epitope** GVPVWREATTLFCASDAKA

**Epitope name** Peptide 2

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6

*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2k, H2-d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was highly reactive in 10/10 BALB/c mice tested, but only in 5/10 CBA/J mice.

**HXB2 Location** gp160 (42–61)

**Author Location** gp120 (42–61 IIIB)

**Epitope** VPVWKEATTLFCASDAKAY?

**Epitope name** A2

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, mean SI = 6.6.

**HXB2 Location** gp160 (52–71)  
**Author Location** gp120 (52–71 IIIB)  
**Epitope** LFCASDAKAYDTEVHNVWAT?

**Epitope name** A3  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human

- References** Geretti *et al.* 1994
- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
  - After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
  - IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
  - 3/15 responders recognized this peptide, mean SI = 4.3.

**HXB2 Location** gp160 (61–80)  
**Author Location** gp120 (60–79 89.6)  
**Epitope** YDTEVHNVWATHACVPTDPN

**Epitope name** Peptide 4  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse  
**Donor MHC** H-2k, H2-d  
**Keywords** epitope processing, immunodominance  
**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was highly reactive in 4/10 BALB/c mice tested, but only in 1/10 CBA/J mice.

**HXB2 Location** gp160 (62–80)  
**Author Location** gp120 (62–80 IIIB)

**Epitope** DTEVHNVWATHACVPTDPN?

**Epitope name** A4  
**Subtype** B  
**Immunogen** HIV-1 infection

- Species (MHC)** human  
**References** Geretti *et al.* 1994
- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
  - After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
  - IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
  - 1/15 responders recognized this peptide, SI = 3.5.

**HXB2 Location** gp160 (62–81)  
**Author Location** gp120 (MN)  
**Epitope** DTEVHNVWATQACVPTDPNP

**Epitope name** DP20  
**Subtype** B  
**Immunogen** HIV-1 infection

- Species (MHC)** human (DR)  
**Assay type** Cytokine production, proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** HAART, ART, acute/early infection, cross-presentation by different HLA

- References** Malhotra *et al.* 2003
- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymphoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
  - This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail. The CD4+ clones showed MHC-restricted cytotoxicity and secreted high levels of cytokines when stimulated. These Th responses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.
  - This peptide showed bound to HLA-DRB1\*0101.

**HXB2 Location** gp160 (65–75)  
**Author Location** gp120 (72–82)  
**Epitope** AHKVVWATHACV

**Immunogen** vaccine  
*Vector/Type:* peptide  
**Species (MHC)** mouse (H-2<sup>b<sub>xk</sub></sup>, H-2<sup>s<sub>xd</sub></sup>)

- References** Sastry & Arlinghaus 1991
- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

**HXB2 Location** gp160 (74–85)  
**Author Location** gp120 (81–92)  
**Epitope** CVPTNPVPQEVV  
**Immunogen** vaccine  
*Vector/Type:* peptide  
**Species (MHC)** mouse (H-2<sup>bxk</sup>, H-2<sup>sxd</sup>)  
**References** Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

**HXB2 Location** gp160 (74–85)  
**Author Location** gp120 (74–85 LAI)  
**Epitope** CVPTDNPQEVV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** gp160 (80–99)  
**Author Location** gp120 (51–70 HXB2)  
**Epitope** NPQEVVLVNTENFNMWKNKND  
**Subtype** B  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**Keywords** TCR usage  
**References** Li Pira *et al.* 1998

- Clonal heterogeneity was broad for a recall response to tetanus toxoid or PPD, but oligoclonal to primary HIV antigens, dominated in this case by TCR V $\beta$  13 usage.
- Donor of PBMC that recognized this epitope had HLA-DR alleles 2 and 7.

**HXB2 Location** gp160 (81–100)  
**Author Location** gp120 (80–99 89.6)  
**Epitope** PQEVVVLGNVTENFNMWKNMM  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse (H-2<sup>k</sup>)  
**Keywords** immunodominance  
**References** Dai *et al.* 2001

- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2<sup>k</sup> and BALB/c H-2<sup>d</sup> mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
- This peptide was recognized by 10/10 CBA/J with an average SI of 8.2, and not by BALB/c mice, so is considered to be uniquely immunodominant for H-2<sup>k</sup>
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

**HXB2 Location** gp160 (81–100)  
**Author Location** gp120 (80–99 89.6)  
**Epitope** PQEVVVLGNVTENFNMWKNMM  
**Epitope name** Peptide 6  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse  
**Donor MHC** H-2k  
**Keywords** epitope processing, immunodominance  
**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was not reactive in any BALB/c mice tested (0/10), but was highly reactive in all (10/10) CBA/J mice.

**HXB2 Location** gp160 (81–101)  
**Author Location** gp120 (81–101 IIIB)  
**Epitope** PQEVVVLNVNTENFNMWKNMVMV?  
**Epitope name** B1  
**Subtype** B

**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, mean SI = 5.1.

**HXB2 Location** gp160 (92–101)  
**Author Location** gp120 (90–100 W6.ID)  
**Epitope** YFNMWKNMMV

**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade W61D  
*HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21

**Species (MHC)** human  
**References** Jones *et al.* 1999

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated.
- One T-cell clone reacts with two overlapping peptides, and the region of overlap is: YFNMWKNMMV.
- The first 20-mer peptide that this clone reacts with is PQEVVVLGNVTEYFNMWKNMMV, and the IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version: IIIB: pgevvlvntvteNfDmwknDmv.

**HXB2 Location** gp160 (92–111)  
**Author Location** gp120 (92–111 W6.ID)  
**Epitope** YFNMWKNMVDQMHEIISL  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21

**Species (MHC)** human  
**References** Jones *et al.* 1999

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated.
- The IIIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version of the peptide NfDmwknDmvEqmhediisl.
- Six T-cell lines react with this peptide, but some of these can also be stimulated by other gp120 peptides located in different regions of gp120.

**HXB2 Location** gp160 (101–126)  
**Author Location** gp120 (101–126)  
**Epitope** VEQMHEIISLWDQSLKPCVKLTPLC  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>k</sup>)  
**References** Sjolander *et al.* 1996

- Study showing that T-cell determinants from glycoproteins can be dependent on the glycosylation of the protein.

**HXB2 Location** gp160 (102–114)  
**Author Location** gp120 (109–121)  
**Epitope** EQMHEDIISLWDQ  
**Immunogen** vaccine  
*Vector/Type:* peptide

**Species (MHC)** mouse (H-2<sup>bxk</sup>)  
**References** Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

**HXB2 Location** gp160 (102–116)  
**Author Location** gp160 (109–123 IIIIB)  
**Epitope** EQMHEDIISLWDQSL  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)  
**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- B10.D2 (H-2A<sup>d</sup>, E<sup>d</sup>) and B10.A(R5) (H-2A<sup>b</sup>, E<sup>b</sup>) mice immunized with rec gp160 showed a proliferative response to EQMHEDIISLWDQSL.
- EQMHEDIISLWDQSLKPCVK encompasses several murine Th epitopes including HEDIISLWDQSLK and is referred to as a "multideterminant region" or cluster peptide.

**HXB2 Location** gp160 (102–116)  
**Author Location** gp120 (109–123 IIIIB)  
**Epitope** EQMHEDIISLWDQSL

**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIIB *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>15</sup>)  
**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (102–121)  
**Author Location** gp160 (109–128 IIIIB)  
**Epitope** EQMHEDIISLWDQSLKPCVK  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* protein *Strain:* B clade IIIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** human, mouse (H-2<sup>k</sup>, H-2<sup>s</sup>)  
**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- EQMHEDIISLWDQSLKPCVK encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
- This cluster peptide elicited proliferative responses in cells from vaccinated B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>) and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>), while shorter peptides from within this region stimulated H-2<sup>k</sup>, H-2<sup>d</sup> and H-2<sup>b</sup> responses, but not H-2<sup>s</sup>
- IL-2 production was observed in response to this peptide in 64% (23/36) of asymptomatic HIV-infected individuals.

**HXB2 Location** gp160 (102–121)  
**Author Location** gp120 (102–121 IIIIB)  
**Epitope** EQMHEDIISLWDQSLKPCVK?  
**Epitope name** B3  
**Subtype** B  
**Immunogen** HIV-1 infection

**Species (MHC)** human  
**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 5.9.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp120 (112–124 IIIIB)  
**Epitope** HEDIISLWDQSLK  
**Epitope name** T2  
**Immunogen** vaccine  
*Strain:* B clade IIIIB *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>k</sup>)

- References** Hale *et al.* 1989
- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp160 (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2<sup>k</sup>)

**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- B10.BR (H-2A<sup>k</sup>, E<sup>k</sup>) mice immunized with rec gp160 showed a strong proliferative response to three overlapping peptides, QMHEDIISLWDQSL, HEDIISLWDQSLK, and DIISLWDQSLKPCVK, and HEDIISLWDQSLK is common to between them.
- EQMHEDIISLWDQSLKPCVK encompasses several murine Th epitopes including HEDIISLWDQSLK and is referred to as a "multideterminant region" or cluster peptide.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp120 (112–124 BH10)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen** computer prediction

**Species (MHC)** mouse (H-2<sup>k</sup>, H-2<sup>s</sup>)

**References** Cease *et al.* 1987

- 1 of 2 functional epitopes identified using an amphipathic helix epitope prediction algorithm.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp120 (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Clerici *et al.* 1997

- Used in a study of pentoxifylline's influence on HIV specific T-cells.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp120 (112–124 BH10)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* gp160

**Species (MHC)** human

**References** Berzofsky *et al.* 1988

- Proliferative response to T1 and T2 peptides in 14 immunized, uninfected humans.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp120 (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Clerici *et al.* 1989

- IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp120 (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Clerici *et al.* 1991a

- Peptides stimulate Th cell function and CTL activity in similar patient populations.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp120 (112–124)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160

**Species (MHC)** human

**References** Clerici *et al.* 1991b

- Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp120 (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen**

**Species (MHC)** human

**References** Clerici *et al.* 1992

- Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp120 (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen** vaccine

*Vector/Type:* peptide prime with protein boost *Strain:* B clade IIIB *HIV component:* gp160

**Species (MHC)** macaque

**References** Hosmalin *et al.* 1991

- Peptide priming to induce T-cell help enhances antibody response to gp160 immunization.

**HXB2 Location** gp160 (105–117)  
**Author Location** gp120 (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen**

**Species (MHC)** human

**References** Pinto *et al.* 1995

- CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers.

**HXB2 Location** gp160 (105–117)

**Author Location** gp120 (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Kaul *et al.* 1999

- Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- Helper epitopes used in this study were noted to be previously described Clerici *et al.* [1989], and were not explicitly described in Kaul *et al.* [1999]

**HXB2 Location** gp160 (105–117)

**Author Location** gp120

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human

**Keywords** subtype comparisons, responses in children, mother-to-infant transmission

**References** Kuhn *et al.* 2001a

- In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4.
- The mothers were predominantly infected with subtype C, but the T help response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents.
- 3/33 infants with cord blood T help responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected. 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breastfeeding.
- Measurable HIV specific T help responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1.

**HXB2 Location** gp160 (105–117)

**Author Location** Env (112–124 IIIB)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Subtype** B

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)**

**Assay type** Cytokine production

**Keywords** mother-to-infant transmission

**References** Clerici *et al.* 1993a

- Cord blood samples in 8/23 infants with HIV+ mothers showed IL-2 production in response to peptides from HIV-1 gp1260, demonstrating that Th cell priming to HIV env determinants can occur in utero. HIV-specific Th immunity in utero may be protective, as none of the 8 with HIV-1 specific Th activity became infected, while 3/15 infants with no detectable Th activated were infected.

- PBL from 10/21 of the mothers showed HIV-1 specific Th activity through IL-2 production in response to Env peptides.

**HXB2 Location** gp160 (105–117)

**Author Location** Env (IIIB)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)**

**Assay type** Cytokine production

**References** Clerici *et al.* 1994a

- Six of eight HIV-exposed health care workers had transient HIV-specific T-helper responses after percutaneous exposure to HIV, responding to two or more Env peptides among the set T1, T2, Th4.1, P18IIIB and P18MN. Responses were lost after 12–56 weeks. The HIV-specific Th responses occurred without seroconversion or PCR evidence for infection.
- Six of the eight HIV-exposed individuals responded to two or more peptides, whereas, only one individual exposed to HIV-negative blood responded to one peptide.

**HXB2 Location** gp160 (105–117)

**Author Location** HIV-1 (IIIB)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)**

**Assay type** Cytokine production

**References** Clerici *et al.* 1994b

- IL-10-specific mRNA was upregulated in PBMC from asymptomatic, HIV-infected (HIV+) patients, and was particularly high in those with severely compromised Th cells function. Th response to HIV peptides *in vitro* could be restored by IL-10 Ab.

**HXB2 Location** gp160 (105–117)

**Author Location** Env (112–124)

**Epitope** HEDIISLWDQSLK

**Epitope name** T2

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** proliferation

**Keywords** responses in children, mother-to-infant transmission

**References** Kuhn *et al.* 2001b

- T helper proliferative responses in cord blood at delivery to a cocktail of HIV envelope peptides were infrequent (1/41) among infants whose HIV-positive mothers received antiretroviral prophylaxis at delivery to prevent transmission. Responses were 10 times more frequent among infants of HIV-seropositive women who had no antiretroviral treatment (7/29). Reductions of HIV-specific responses occurred despite persistence of detectable HIV RNA in the mothers at delivery.
- The reduction of Th responses in newborns raises the possibility that anti-retroviral exposure during pregnancy may block subsequent immune protection. The authors point two relevant citations that showed ARV exposed infants had a more rapid course of progression (Kuhn *et al.*, JID 182:104 (2000)), but

were at no greater risk of infection due to subsequent breast feeding (Ditrane *et al.*, Lancet 354:2050 (1999)).

- HXB2 Location** gp160 (105–117)  
**Author Location** Env (gp160) (105–117)  
**Epitope** HEDIISLWDQSLK  
**Epitope name** TH2  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** South Africa  
**Assay type** proliferation  
**Keywords** responses in children, variant cross-recognition or cross-neutralization  
**References** Meddows-Taylor *et al.* 2004
- Viral isolates (gp160) from 16 vertically HIV-1 infected children (8 T-helper cell Env responders and 8 non-responders) were analyzed for variation after comparison with Env peptide sequences (conserved regions T1, T2 and TH4.1, hyper-variable regions P18 MN and P181 IIIB) used for in vitro stimulation.
  - T2 was the most conserved of the 5 peptides studied.
  - No correlation between the age, clinical category (mild or severe), HIV-1 viral load and the degree of epitope variation was established.

- HXB2 Location** gp160 (105–123)  
**Author Location** gp120 (112–130 IIIB)  
**Epitope** HEDIISLWDQSLKPCVKLT  
**Immunogen**  
**Species (MHC)** human  
**References** Furci *et al.* 1997
- 9/11 exposed-uninfected individuals in this study had a proliferative response to a C5 peptide, but none reacted with this previously defined epitope.

- HXB2 Location** gp160 (108–119)  
**Author Location** gp120 (108–119 LAI)  
**Epitope** IISLWDQSLKPC  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Schrier *et al.* 1989
- Stimulates T-cell proliferation in HIV-infected donors.

- HXB2 Location** gp160 (108–119)  
**Author Location**  
**Epitope** IISLWDQSLKPC  
**Immunogen**  
**Species (MHC)**  
**Keywords** subtype comparisons, viral fitness and reversion  
**References** de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
  - Present in 45/51 Brazilian sequences.

- HXB2 Location** gp160 (110–125)  
**Author Location** gp120 (110–125)

- Epitope** SLWDQSLKPCVKLTPL  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** rate of progression  
**References** Caruso *et al.* 1997
- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71.
  - The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost.
  - This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24.

- HXB2 Location** gp160 (110–125)  
**Author Location**  
**Epitope** SLWDQSLKPCVKLTPL  
**Immunogen**  
**Species (MHC)**  
**Keywords** subtype comparisons, viral fitness and reversion  
**References** de Queiroz *et al.* 2007
- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
  - Present in 47/51 Brazilian sequences.

- HXB2 Location** gp160 (111–123)  
**Author Location** gp120 (118–130)  
**Epitope** LWDQSLKPCVKLT  
**Immunogen** vaccine  
**Vector/Type:** peptide  
**Species (MHC)** macaque  
**References** Nehete *et al.* 1993
- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
  - Proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys.

- HXB2 Location** gp160 (112–130)  
**Author Location** gp120 (112–130 IIIB)  
**Epitope** WDQSLKPCVKLTPLCVSLK?  
**Epitope name** B4  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Geretti *et al.* 1994
- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
  - After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.

- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 4.4.

**HXB2 Location** gp160 (112–141)

**Author Location** gp120 (112–141 NL43)

**Epitope** WDQSLKPCVKLTPLCVSLKCTDLGNATNTN

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade NL43

*HIV component:* gp120, gp160

**Species (MHC)** human

**References** Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- Over 35% of vaccinees had a stimulation index of greater than 5 to this peptide.

**HXB2 Location** gp160 (115–126)

**Author Location** gp120 (115–126 LAI)

**Epitope** SLKPCVKLTPLC

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** gp160 (115–129)

**Author Location** gp120 (115–129 LAI)

**Epitope** SLKPCVKLTPLCVSL

**Subtype** B

**Immunogen** peptide-HLA interaction

**Species (MHC)** human (HLA-DR)

**Keywords** binding affinity

**References** Gaudebout *et al.* 1997

- Peptide bound to both HLA-DR\*1101 and HLA-DR\*0401 with high affinity.
- Because of the distinctive binding pockets of HLA-DR\*1101 and HLA-DR\*0401, peptides that bound both were considered candidates for promiscuous HLA-DR binding.

**HXB2 Location** gp160 (121–140)

**Author Location** gp120 (120–139 89.6)

**Epitope** KLTPLCVTLNCTNLNITKNT

**Epitope name** Peptide 10

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6

*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences

Th antigen processing and the frequency of immunogenic sequences.

- This peptide was highly reactive in 5/10 BALB/c mice tested, but not in and (0/10) CBA/J mice.

**HXB2 Location** gp160 (121–141)

**Author Location** gp120 (131–151 IIIB)

**Epitope** KLTPLCVSLKCTDLKNDTNTN?

**Epitope name** C1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 3.9.

**HXB2 Location** gp160 (122–141)

**Author Location** gp120 (121–140 MN)

**Epitope** LTPLCVTLNCTDLRNTTNTN

**Epitope name** 1931

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, protein *Strain:* B clade

MN *HIV component:* gp120 *Adjuvant:*

Complete Freund's Adjuvant (CFA)

**Species (MHC)** guinea pig

**Keywords** vaccine-specific epitope characteristics, Th1

**References** Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensitivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensitivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 3/5 animals vaccinated with rec gp120 responded by DTH to this peptide, while 0/6 vaccinated with plasmid gp120 DNA responded.

**HXB2 Location** gp160 (122–141)

**Author Location** gp120 (122–141 IIIB)

**Epitope** LTPLCVSLKCTDLKNDTNTN?

**Epitope name** B5

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994



- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- 1/15 responders recognized this peptide, SI = 3.1.

**HXB2 Location** gp160 (136–155)

**Author Location** gp120 (141–160 MN)

**Epitope** NSTAWNNSNSEGTIKGGEMK

**Epitope name** 1932

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** guinea pig

**Keywords** vaccine-specific epitope characteristics, Th1

**References** Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensitivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensitivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 4/5 animals vaccinated with rec gp120 responded by DTH to this peptide, as did 2/6 vaccinated with plasmid gp120 DNA.

**HXB2 Location** gp160 (138–159)

**Author Location** gp120 (141–160 W6.ID)

**Epitope** TTSNGWTGEIRKGEIKNCSF

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21

**Species (MHC)** human

**References** Jones *et al.* 1999

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated.
- The IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version of the peptide: IIIB: tsnSSGRMIMEgeikncsf.

**HXB2 Location** gp160 (142–161)

**Author Location** gp120 (142–161 IIIB)

**Epitope** SSSGRMIMEKGEIKNCSFNI?

**Epitope name** C2

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** immunodominance

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Five peptides were recognized most frequently: C2 (aa 142–161), C3 (aa 152–171), C5 (aa 172–191), E5 (aa 272–291) and G4 (aa 380–393). The first three were in or near V2, the other two were proximal to the V3 and V4 loops.
- 4/15 responders recognized this immunodominant peptide, average SI = 4.3.

**HXB2 Location** gp160 (147–168)

**Author Location** gp120 (152–173 NL43)

**Epitope** MMEKGEIKNCSFNISTSIRGK

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade NL43 *HIV component:* gp120, gp160

**Species (MHC)** human

**References** Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- Over 50% of vaccinees had a stimulation index of greater than 5 to this peptide.

**HXB2 Location** gp160 (152–171)

**Author Location** gp120 (152–171 IIIB)

**Epitope** GEIKNCSFNISTSIRGKVQK?

**Epitope name** C3

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** immunodominance

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Five peptides were recognized most frequently: C2 (aa 142–161), C3 (aa 152–171), C5 (aa 172–191), E5 (aa 272–291) and G4 (aa 380–393). The first three were in or near V2, the other two were proximal to the V3 and V4 loops.
- 4/15 responders recognized this immunodominant peptide, average SI = 4.4.

- HXB2 Location** gp160 (155–169)  
**Author Location** Env (UG92005)  
**Epitope** KNCSFNITTELIDKK  
**Immunogen** vaccine  
*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)
- Species (MHC)** mouse (H-2 IA<sup>b</sup>)  
**Keywords** subtype comparisons, epitope processing, TCR usage  
**References** Surman *et al.* 2001
- This epitope is located in the V2 region of UG92005 (UG, clade D) and the hybridoma that recognized it used Vβ5.
  - C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3–4 weeks later boosted with VV, and 3–4 weeks later boosted again with purified protein in Freund's adjuvant.
  - The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
  - Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and Vβ usage was determined.
  - Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
  - 80 unique clonotypes were characterized from six mice.
  - H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
  - Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.
- HXB2 Location** gp160 (155–169)  
**Author Location** gp120 (160–174 LAI)  
**Epitope** KNCSFNISTIRGKV  
**Subtype** B  
**Immunogen**  
**Species (MHC)** human (HLA-DR)  
**Keywords** binding affinity  
**References** Gaudebout *et al.* 1997
- Peptide binds to both HLA-DR\*1101 and HLA-DR\*0401 with high affinity.
  - Because of the distinctive binding pockets of HLA-DR\*1101 and HLA-DR\*0401, peptides that bound both were considered candidates for promiscuous HLA-DR binding.
- HXB2 Location** gp160 (159–178)  
**Author Location** gp120 (160–179 89.6)

- Epitope** FYITTSIRNKVKKEYALFNR  
**Epitope name** Peptide 14  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)
- Species (MHC)** mouse  
**Donor MHC** H-2k, H2-d  
**Keywords** epitope processing, immunodominance  
**References** Dai *et al.* 2001
- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
  - This peptide was highly reactive in 6/10 BALB/c mice tested, and in 4/10 CBA/J mice.
- HXB2 Location** gp160 (162–181)  
**Author Location** gp120 (162–181 IIIB)  
**Epitope** STSIRGKVQKEYAFFYKLDI  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade IIIB  
*HIV component:* Env
- Species (MHC)** macaque  
**References** Lekutis *et al.* 1997
- HIV-1 env DNA vaccine induced Th cell response to this epitope in a rhesus monkeys.
- HXB2 Location** gp160 (162–182)  
**Author Location** gp120 (162–182 IIIB)  
**Epitope** STSIRGKVQKEYAFFYKLDII?  
**Epitope name** C4  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Geretti *et al.* 1994
- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
  - After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
  - IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
  - 1/15 responders recognized this peptide, SI = 3.3.
- HXB2 Location** gp160 (166–185)  
**Author Location** gp120 (MN)  
**Epitope** RDKMQKEYALLYKLDIVSID  
**Epitope name** RD20  
**Subtype** B  
**Immunogen** HIV-1 infection

**Species (MHC)** human**Assay type** Cytokine production, proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining**Keywords** HAART, ART, acute/early infection**References** Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymphoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail. These Th responses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.

**HXB2 Location** gp160 (169–189)**Author Location** gp120 (141–160 W6.ID)**Epitope** VQKEYALFYNLDDVVPIDDDNA**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21**Species (MHC)** human**References** Jones *et al.* 1999

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated.
- The IIIB version of this peptide does not induce proliferation in the T-cell line that responds to the W61D version of the peptide —F–K–II–N–TT vqkeyaFfyKldIIPidNdTT.
- Two T-cell lines react specifically with this peptide.

**HXB2 Location** gp160 (172–191)**Author Location** gp120 (172–191 IIIB)**Epitope** EYAFFYKLDIIPIDNDTTSY**Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade IIIB *HIV component:* Env**Species (MHC)** macaque**References** Lektus *et al.* 1997

- HIV-1 env DNA vaccine induced Th cell response to this epitope in a rhesus monkey.

**HXB2 Location** gp160 (172–191)**Author Location** gp120 (172–191 IIIB)**Epitope** EYAFFYKLDIIPIDNDTTSY?**Epitope name** C5**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** immunodominance**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Five peptides were recognized most frequently: C2 (aa 142–161), C3 (aa 152–171), C5 (aa 172–191), E5 (aa 272–291) and G4 (aa 380–393). The first three were in or near V2, the other two were proximal to the V3 and V4 loops.
- 4/15 responders recognized this immunodominant peptide, average SI = 7.4.

**HXB2 Location** gp160 (174–185)**Author Location** gp160 (174–185 clade B consensus)**Epitope** ALFYKLDVVPID**Subtype** B**Immunogen** HIV-1 infection, computer prediction**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1302)**Country** Brazil**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was ALFYKLDVVPID, shorter FYKLDVVPID peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** gp160 (175–189)**Author Location** Env (UG92005)**Epitope** LFYKLDVVQIDNSTN**Immunogen** vaccine*Vector/Type:* DNA, protein, vaccinia *Strain:* B clade 1007, D clade UG92005 *HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (H-2 IA<sup>b</sup>)**Keywords** subtype comparisons, epitope processing, TCR usage**References** Surman *et al.* 2001

- This epitope is located in the V2 region of UG92005 (UG, clade D) and the V $\beta$  usage of the TCR was not determined.

- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (186–208)  
**Author Location** Env  
**Epitope** NDNTSYRLISCNTSVITQACPKV  
**Epitope name** HIV\_env\_DRB0101\_3  
**Subtype** M  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** United States  
**Assay type** T-cell Elispot  
**Keywords** computational epitope prediction  
**References** De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 5/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DRB0101 sequence of this peptide was YRLISCNTS.

**HXB2 Location** gp160 (186–215)  
**Author Location** gp120 (191–220 NL43)  
**Epitope** NDTTSYTLTSCNTSVITQACPKVSFPEIPI  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* gp120, gp160  
**Species (MHC)** human  
**References** Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- Over 30% of vaccinees had a stimulation index of greater than 5 to this peptide.

**HXB2 Location** gp160 (188–201)  
**Author Location** gp160 (188–201 clade B consensus)  
**Epitope** NTSYRLISCNTSVI  
**Subtype** B  
**Immunogen** HIV-1 infection, computer prediction  
**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1302, DRB1\*1501, DRB5\*0101)  
**Country** Brazil  
**Assay type** CD4 T-cell Elispot - IFNγ, HLA binding  
**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA  
**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was NTSYRLISCNTSVI, shorter YRLISCNTSVI peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** gp160 (188–207)  
**Author Location** gp120 (190–209 89.6)  
**Epitope** NTKYRLISCNTSVITQACPK  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)  
**Species (MHC)** mouse (H-2<sup>k</sup>)  
**Keywords** immunodominance  
**References** Dai *et al.* 2001

- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2<sup>k</sup> and BALB/c H-2<sup>d</sup> mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
- This peptide was recognized by 9/10 CBA/J with an average SI of 9.8, one of the two immunodominant peptides in CBA/J mice, and not by BALB/c mice, so is considered to be uniquely immunodominant for H-2<sup>k</sup>
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

**HXB2 Location** gp160 (188–207)  
**Author Location** gp120 (89.6)  
**Epitope** NTKYRLISCNTSVITQACPK  
**Epitope name** Peptide 17  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2k, H2-d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in only 1/10 BALB/c mice tested, but was one of the most reactive in CBA/J mice, reacting with 9/10 mice.

**HXB2 Location** gp160 (190–212)

**Author Location** Env (185–215)

**Epitope** SYRLISCVITQACPKVSFEP

**Epitope name** HIV\_env\_DRB0101\_62

**Subtype** M

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** T-cell Elispot

**Keywords** computational epitope prediction

**References** De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 1/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DR B0101 sequence of this peptide was NTSVITQA.

**HXB2 Location** gp160 (192–211)

**Author Location** gp120 (192–211 IIIB)

**Epitope** KLTSCNTSVITQACPKVSFE?

**Epitope name** D2

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.

- 1/15 responders recognized this peptide, SI = 3.6.

**HXB2 Location** gp160 (193–218)

**Author Location** gp120 (193–218)

**Epitope** LTSCNSVITQACPKVSFEPIPIHYC

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)

**References** Sjolander *et al.* 1996

- Study showing that T-cell determinants from glycoproteins can be dependent on the glycosylation of the protein.

**HXB2 Location** gp160 (198–212)

**Author Location** Env (1007)

**Epitope** TSVITQACPKVSFEP

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)

**Keywords** subtype comparisons, epitope processing, TCR usage

**References** Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and the Vβ usage of the TCRs for two clonotypes was Vβ3 and Vβ8.1-2.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3–4 weeks later boosted with VV, and 3–4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (198–215)

**Author Location** Env (1007)

**Epitope** TSVITQACPKVSFEPIPI**Immunogen** vaccine*Vector/Type:* DNA, protein, vaccinia*Strain:* B clade 1007, D clade UG92005*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (H-2 IA<sup>b</sup>)**Keywords** subtype comparisons, epitope processing, TCR usage**References** Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and the V $\beta$  usage of the TCR was V $\beta$ 6.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (199–211)**Author Location** gp120 (204–216)**Epitope** SVITQACSKVSFE**Immunogen** vaccine*Vector/Type:* peptide**Species (MHC)** mouse (H-2<sup>bxk</sup>, H-2<sup>sxd</sup>)**References** Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response in mice representing four haplotypes.

**HXB2 Location** gp160 (199–211)**Author Location** Env (204–216)**Epitope** SVITQACSKVSFE**Immunogen** vaccine*Vector/Type:* peptide**Species (MHC)** macaque**References** Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- A weak or transient proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys.

**HXB2 Location** gp160 (199–211)**Author Location** Env (204–216)**Epitope** SVITQACSKVSFE**Immunogen** HIV-1 infection**Species (MHC)** human, chimpanzee**References** Nehete *et al.* 1998b

- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env.

**HXB2 Location** gp160 (200–214)**Author Location** gp120 (205–219 LAI)**Epitope** VITQACPKVSFEPIP**Subtype** B**Immunogen** peptide-HLA interaction**Species (MHC)** human (HLA-DR)**Keywords** binding affinity**References** Gaudebout *et al.* 1997

- Peptide binds to both HLA-DR\*1101 and HLA-DR\*0401 with high affinity.
- Because of the distinctive binding pockets of HLA-DR\*1101 and HLA-DR\*0401, peptides that bound both were considered candidates for promiscuous HLA-DR binding.

**HXB2 Location** gp160 (201–212)**Author Location** Env (1007)**Epitope** ITQACPKVSFEP**Immunogen** vaccine*Vector/Type:* DNA, protein, vaccinia*Strain:* B clade 1007, D clade UG92005*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (H-2 IA<sup>b</sup>)**Keywords** subtype comparisons, epitope processing, TCR usage**References** Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and the V $\beta$  usage of the TCR was V $\beta$ 3.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (TSVITQACPKVSFEP and ITQACPKVSFEPIPI)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.

- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (206–220)

**Author Location** Env (1007)

**Epitope** PKVSFEPIPIHYCAP

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)

**Keywords** subtype comparisons, epitope processing

**References** Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and 12 hybridomas recognized the peptide with V $\beta$  usage of V $\beta$ 4,6,7,8,1-2,8,3,11,12 and others not determined.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be

influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (206–220)

**Author Location** Env (gp160)

**Epitope** PKVSFEPIPIHYCAP

**Subtype** B, D

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H2b)

**Assay type** Cytokine production, CD4 T-cell Elispot - IFN $\gamma$

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Zhan *et al.* 2004

- To develop a polyvalent Env vaccine, subtype specific B and D T-helper epitopes were identified, and mixtures of strain 1007, clade B, or UG92005, clade D envelopes were given to C57BL/6J mice. Mice were intramuscularly immunized with recombinant DNA, then intraperitoneally with rVV and finally with env protein in CFA. A dilution of 1/100 could still elicit type specific responses, and responses persisted with different prime boost combinations.
- Priming with 1007 and UG92005 env's induced both Env-specific (SNNTVGNPIILPCR1 and AMYAPPIAGLIQCSS) and cross-reactive (PKVSFEPIPIHYCAP, C2, GNIRQAHC-NVSKAKW, V3-C3) Th responses in murine spleen cells.

**HXB2 Location** gp160 (206–225)

**Author Location** gp120 (211–230 MN)

**Epitope** PKISFEPIPIHYCAPAGFAI

**Epitope name** 1957

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** guinea pig

**Keywords** vaccine-specific epitope characteristics, Th1

**References** Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensitivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensitivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 5/5 animals vaccinated with rec gp120 responded by DTH to this peptide, as did 2/6 vaccinated with plasmid gp120 DNA.

**HXB2 Location** gp160 (206–230)

**Author Location** gp120 (206–230)

- Epitope** PKVSFEPIPIHYCAPAGFAILKCNN  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)  
**References** Sjolander *et al.* 1996
- Study showing that T-cell determinants from glycoproteins can be dependent on the glycosylation of the protein.
- HXB2 Location** gp160 (208–218)  
**Author Location** Env (UG92005)  
**Epitope** ITFEPIPIHYC  
**Immunogen** vaccine  
*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (H-2 IA<sup>b</sup>)  
**Keywords** subtype comparisons, epitope processing  
**References** Surman *et al.* 2001
  - This epitope is located in the C2 region of UG92005 (UG, clade D) and its was recognized by two hybridomas with V $\beta$  usage V $\beta$ 12 and not determined.
  - The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (PKITFEPIPIHYCAP and ITFEPIPIHYCAPAG)
  - C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
  - The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
  - Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
  - Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
  - 80 unique clonotypes were characterized from six mice.
  - H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
  - Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (208–222)  
**Author Location** Env (UG92005)  
**Epitope** ITFEPIPIHYCAPAG  
**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

- Species (MHC)** mouse (H-2 IA<sup>b</sup>)  
**Keywords** subtype comparisons, epitope processing, TCR usage  
**References** Surman *et al.* 2001
- This epitope is located in the C2 region of UG92005 (UG, clade D) and it was recognized by five hybridomas with V $\beta$  usage V $\beta$ 5, 8.2, 12 and not determined.
  - C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
  - The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
  - Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
  - Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
  - 80 unique clonotypes were characterized from six mice.
  - H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
  - Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.
- HXB2 Location** gp160 (208–227)  
**Author Location** gp120 (210–229 89.6)  
**Epitope** VSFQPIPIHYCVPAGFAMLK  
**Epitope name** Peptide 19  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)  
**Species (MHC)** mouse  
**Donor MHC** H-2k, H2-d  
**Keywords** epitope processing, immunodominance  
**References** Dai *et al.* 2001
  - Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences



Th antigen processing and the frequency of immunogenic sequences.

- This peptide was reactive in 6/10 BALB/c mice tested, and in 6/10 CBA/J mice.

**HXB2 Location** gp160 (209–220)

**Author Location** gp120 (MN)

**Epitope** SFPEIPIHYCAP

**Epitope name** SP12

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR)

**Assay type** Cytokine production, proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** HAART, ART, vaccine-specific epitope characteristics, acute/early infection, cross-presentation by different HLA

**References** Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymphoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail. The CD4+ clones showed MHC-restricted cytotoxicity and secreted high levels of cytokines when stimulated. These Th responses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.
- Seven out of 12 clones recognized this conserved C3 region of gp120. Clone one was mapped to the optimal epitope and was found to be presented by HLA-DR. The peptide showed promiscuous binding to DRB1\*0101, DRB1\*0401, DRB1\*1302, DRB1\*0701, DRB1\*0901, DRB4\*0101, DRB5\*0101.

**HXB2 Location** gp160 (210–218)

**Author Location** Env (186–194 1035)

**Epitope** FEPIPIHYC

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* vaccinia prime with gp120 boost *Strain:* B clade 1035 *HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (Class II I Ab)

**Assay type** proliferation, T-cell Elispot

**Keywords** epitope processing, vaccine-induced epitopes, escape, TCR usage

**References** Zhan *et al.* 2003

- A very narrow Th response was stimulated in C57BL/6 mice vaccinated with vaccinia expressed HIV-1 env clone 1035.

Five of seven different Th hybridomas isolated from five immunized mice immunized reacted with the peptide PKVS-FEPIPIHYCAP, located in the C2 region of gp120. TCR V $\beta$  usage indicated each of the clones was unique. Splenic populations from other C57BL/6 mice immunized with 1035 env confirmed that the gp120 specific T-helper response was focused on the PKVSFEPIPIHYCAP peptide. The authors suggest the protein structural context may contribute to the immunodominance of this peptide.

- The minimal epitope was mapped for one of the hybridomas, and was FEPIPIHYC.
- The natural variant, fDpipihyc, did not stimulate a response in three of the hybridomas.

**HXB2 Location** gp160 (210–223)

**Author Location** gp120 (215–228)

**Epitope** FEPIPIHYCAFPGF

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse (H-2<sup>b<sub>k</sub></sup>)

**References** Sastry & Arlinghaus 1991

- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

**HXB2 Location** gp160 (212–231)

**Author Location** gp120 (221–240 W6.ID)

**Epitope** PIPHYCAPAGFAILKCNK

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21

**Species (MHC)** human

**References** Jones *et al.* 1999

- An HIV seronegative volunteer was vaccinated with rgp120 and a QS21/MPL adjuvant and HIV-1 specific T-cell lines were isolated.
- Two T-cell lines react specifically with this peptide.

**HXB2 Location** gp160 (212–231)

**Author Location** gp120 (212–231 IIIB)

**Epitope** PIPHYCAPAGFAILKCNK?

**Epitope name** D4

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 4.2.

**HXB2 Location** gp160 (214–220)

**Author Location** Env (1007)**Epitope** PIHYCAP**Immunogen** vaccine*Vector/Type:* DNA, protein, vaccinia*Strain:* B clade 1007, D clade UG92005*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (H-2 IA<sup>b</sup>)**Keywords** subtype comparisons, epitope processing, TCR usage**References** Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and the V $\beta$  usage of the TCR was not determined.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (PKVSFEPIPIHYCAP and PIHYCAPAGFAILKC)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (215–225)**Author Location** Env (1007)**Epitope** IHYCAPAGFAI**Immunogen** vaccine*Vector/Type:* DNA, protein, vaccinia*Strain:* B clade 1007, D clade UG92005*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (H-2 IA<sup>b</sup>)**Keywords** subtype comparisons, epitope processing, TCR usage**References** Surman *et al.* 2001

- This epitope is located in the C2 region of 1007 (US, clade B) and the V $\beta$  usage of the TCR was not determined.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (EPIPIHYCAPAGFAI and IHYCAPAG-FAILKCN)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (216–225)**Author Location** Env (UG92005)**Epitope** HYCAPAGFAI**Immunogen** vaccine*Vector/Type:* DNA, protein, vaccinia*Strain:* B clade 1007, D clade UG92005*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (H-2 IA<sup>b</sup>)**Keywords** subtype comparisons, epitope processing, TCR usage**References** Surman *et al.* 2001

- This epitope is located in the C2 region of UG92005 (UG, clade D) and V $\beta$  usage of its TCR was not determined.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (EPIPIHYCAPAGFAI and HYCAPAG-FAILKCNND)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.

- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (220–234)

**Author Location** gp120 (225–240 SF2)

**Epitope** PAGFAILKCNKTFN

**Immunogen** in vitro stimulation or selection

**Species (MHC)**

**References** Manca *et al.* 1993

- T-cell line derived from unprimed, uninfected individual.
- Responds to APC pulsed with either synthetic peptide or gp120.
- Human MAbs 448-D and 450-D enhance APC gp120 uptake and presentation.

**HXB2 Location** gp160 (220–234)

**Author Location** gp120 (IIIB)

**Epitope** PAGFAILKCNKTFN

**Epitope name** pep24

**Immunogen** vaccine

*Vector/Type:* Streptococcus gordonii *HIV component:* gp120

**Species (MHC)** human

**Keywords** immunodominance

**References** Pozzi *et al.* 1994

- This previously described immunodominant Th cell epitope was fused to the streptococcal surface protein M6 (emm-6.1), for expression on the surface of the bacterium Streptococcus gordonii.
- Recombinant bacteria showed efficient MHC class II mediated presentation of gp120 to T-cells by stimulation of a proliferative response in a human T cell clone specific for pep24.

**HXB2 Location** gp160 (220–235)

**Author Location** gp120 (IIIB)

**Epitope** PAGFAILKCNKTFNY

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DR2)

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.
- gp120 priming induced T-cells that recognize this peptide.

**HXB2 Location** gp160 (220–235)

**Author Location** gp120 (220–235 HXB2)

**Epitope** PAGFAILKCNKTFNY

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DR2)

**Keywords** escape

**References** Guzman *et al.* 1998

- *Listeria monocytogenes*, an intracellular pathogen which is ingested by macrophages and can escape from the phagosome to replicate in the cytoplasm, was used successfully as carrier to deliver this gp120 epitope to CD4+ T-cells.

**HXB2 Location** gp160 (220–235)

**Author Location** gp120 (191–205 HXB2)

**Epitope** PAGFAILKCNKTFNY

**Subtype** B

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DR2)

**References** Fenoglio *et al.* 1999

- gp120 pep24 epitope exhibited antagonistic activity against proliferation of gp120-specific T-cells when flanked by unrelated amino acid sequence.
- The glutathione S-transferase (GST)-peptide system can be used to display peptides; antigenicity was maintained when this peptide was expressed at the C-term end, but antagonism resulted when this peptide was expressed at the N-term end.

**HXB2 Location** gp160 (222–241)

**Author Location** gp120 (222–241 IIIB)

**Epitope** GFAILKCNKTFNGTGPCTN?

**Epitope name** D5

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, average SI = 4.8.

**HXB2 Location** gp160 (223–231)

**Author Location** gp120 (194–202 HXB2)

**Epitope** FAILKCNK

**Subtype** B

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (DR2, DR6)

**References** Manca *et al.* 1996

- Epitope was the minimal stimulatory sequence defined for two Th lines stimulated *in vitro*.
- One Th line was stimulated by gp120, one by a Glutathione-S-transferase (GST)-peptide fusion.
- Alanine substitutions at position 914, 196, and 202 abrogated activity for the GST-peptide stimulated line, but not for a gp120 stimulated line.
- Constructs combining GST and the PAGFAILKCNNKTFNY gp120 peptide at the C-term end of GST stimulated Th cells but not at the N-term end.

**HXB2 Location** gp160 (223–231)

**Author Location** gp120 (194–202 HXB2)

**Epitope** FAILKCNNK

**Subtype** B

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (DR2, DR6)

**References** Manca *et al.* 1996

- Epitope was the minimal stimulatory sequence defined for two Th lines stimulated *in vitro*.
- One Th line was stimulated by p66, one by a Glutathione-S-transferase (GST)-peptide fusion protein.
- Alanine substitutions at position 914, 196, and 202 abrogated activity for the GST-peptide stimulated line, but not for a gp120 stimulated line.
- Constructs linking GST to the PAGFAILKCNNKTFNY gp120 peptide at the C-term end of GST stimulated Th cells, constructs linking at the N-term end did not.
- The C and N termini of GST are not intrinsically permissive or non-permissive, presentation is epitope specific (see SSTVNDIQKLV for contrast)

**HXB2 Location** gp160 (223–231)

**Author Location** gp120 (237–245 SF2, HXB2)

**Epitope** FAILKCNNK

**Immunogen**

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** subtype comparisons, immunodominance

**References** Fenoglio *et al.* 2000

- This peptide is an immunodominant Th epitope in BALB/c mice.
- Substitutions in positions 237, 241, 243, 244 with Ala all cause reduced recognition.
- Most natural analogs they tested did not cross-react, including peptides based on clade A, B, C, D, E and O sequences.
- Position 237 and 244 when substituted with Ala cause an antagonistic response and the natural analogues of this epitope to loose antigenicity.
- Some of the naturally occurring variants also cause an antagonistic response.

**HXB2 Location** gp160 (223–231)

**Author Location** gp120 (238–246 HXB2)

**Epitope** FAILKCNNK

**Subtype** B

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human

**Keywords** TCR usage

**References** Li Pira *et al.* 1998

- Clonal heterogeneity was broad for a recall response to tetanus toxoid or PPD, but oligoclonal to primary HIV antigens, dominated in this case by TCR V $\beta$  22 usage.
- Donor of PBMC that recognized this epitope had HLA-DR alleles 2 and 6.
- The only (detected) immunogenic variant of this epitope was derived from strain NOF (YAILKCNNK)

**HXB2 Location** gp160 (230–245)

**Author Location** gp120 (IIIB)

**Epitope** NKTfNGKGPCTNVSTY

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (232–251)

**Author Location** gp120 (232–251 IIIB)

**Epitope** TFNGTGPCNTVSTVQCTHGI?

**Epitope name** E1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 3.9.

**HXB2 Location** gp160 (235–247)

**Author Location** gp120 (240–252)

**Epitope** GTGPCTNVSTVQC

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** macaque

**References** Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Proliferative response to this peptide was observed in 1/3 immunized rhesus monkeys, with a weak transient response in the other two.

**HXB2 Location** gp160 (238–257)

**Author Location** gp120 (240–249 89.6)

**Epitope** PCTNVSTVQCTHGIRPVVST

**Epitope name** Peptide 22

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was highly reactive in 6/10 BALB/c mice tested, but not in any (0/10) CBA/J mice.

**HXB2 Location** gp160 (240–255)

**Author Location** gp120 (IIIB)

**Epitope** TNVSTVQCTHGRPIY

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.

**HXB2 Location** gp160 (242–261)

**Author Location** gp120 (242–261 IIIB)

**Epitope** VSTVQCTHGIRPVVSTQLLL

**Immunogen** SHIV infection

**Species (MHC)** macaque (DRB1\*0406)

**References** Lekutis & Letvin 1997

- A novel C2 region Th epitope was described in SHIV-89.6 infected Macaca mulatta.

**HXB2 Location** gp160 (242–261)

**Author Location** gp120 (242–261 IIIB)

**Epitope** VSTVQCTHGIRPVVSTQLLL?

**Epitope name** E2

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 3.4.

**HXB2 Location** gp160 (244–266)

**Author Location** Env

**Epitope** TVQCTHGIRPVVSTQLLLNGSLA

**Epitope name** HIV\_env\_DRB0101\_11

**Subtype** M

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** T-cell Elispot

**Keywords** computational epitope prediction

**References** De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 1/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DR B0101 sequence of this peptide was RPVVSTQL.

**HXB2 Location** gp160 (246–268)

**Author Location** Env (438–460)

**Epitope** QCTHGIRPVVSTQLLLNGSLAEE

**Epitope name** HIV\_env\_DRB0101\_02

**Subtype** M

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** T-cell Elispot

**Keywords** computational epitope prediction

**References** De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 1/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DRB0101 sequence within this peptide was PVVSTQLLL.

**HXB2 Location** gp160 (250–265)

**Author Location** gp120 (IIIB)

**Epitope** GIRPIVSTQLLLNGSC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (252–271)

**Author Location** gp120 (252–271 IIIB)

**Epitope** RPVVSTQLLLNGSLAEEVV?

**Epitope name** E3

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, average SI = 7.4.

**HXB2 Location** gp160 (262–281)

**Author Location** gp120 (262–281 IIIB)

**Epitope** NGLAEEEVIRSVNFTDNA?

**Epitope name** E4

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, average SI = 3.1.

**HXB2 Location** gp160 (264–287)

**Author Location** gp120 (269–292 NL43)

**Epitope** SLAEEEVIRSANFTDNAKTIIVQ

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* gp120, gp160

**Species (MHC)** human

**References** Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- 50% of vaccinees had a stimulation index of greater than 5 to this peptide.

**HXB2 Location** gp160 (269–283)

**Author Location** gp120 (269–283 IIIB, B10)

**Epitope** EVVIRSANFTDNAKT

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (269–291)

**Author Location** Env

**Epitope** EVVIRSENFTNNAKTIIVQLNES

**Epitope name** HIV\_env\_DRB0101\_7

**Subtype** M

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** T-cell Elispot

**Keywords** computational epitope prediction

**References** De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 1/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DRB0101 sequence of this peptide was NFTNNAKTI.

**HXB2 Location** gp160 (270–285)

**Author Location** gp120 (IIIB)

**Epitope** VVIRSDNFTNNAKTIC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (272–291)

**Author Location** gp120 (272–291 IIIB)

**Epitope** IRSVNFTDNAKTIIVQLNLS?

**Epitope name** E5

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** immunodominance

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Five peptides were recognized most frequently: C2 (aa 142–161), C3 (aa 152–171), C5 (aa 172–191), E5 (aa 272–291) and G4 (aa 380–393). The first three were in or near V2, the other two were proximal to the V3 and V4 loops.
- 4/15 responders recognized this immunodominant peptide, average SI = 5.0.

**HXB2 Location** gp160 (274–288)

**Author Location** gp120 (274–288 IIIB, B10)

**Epitope** SANFTDNAKTIIIVQL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (274–296)

**Author Location** Env

**Epitope** SENFTNNAKIIIVQLNESVIVN

**Epitope name** HIV\_env\_DRB0101\_5

**Subtype** M

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** T-cell Elispot

**Keywords** computational epitope prediction

**References** De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to select 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to the 9 study peptides.
- 1/26 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DRB0101 sequence of this peptide was AKIIIVQLN.

**HXB2 Location** gp160 (276–295)

**Author Location** gp120 (MN)

**Epitope** NFTDNAKTIIIVHLNESVQIN

**Epitope name** NN20

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** Cytokine production, proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** acute/early infection

**References** Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymphoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail. These Th responses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.

**HXB2 Location** gp160 (280–296)

**Author Location** gp120 (IIIB)

**Epitope** NAKTIIVQLNESVAIC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (288–307)

**Author Location** gp120 (290–309 89.6)

**Epitope** LNESVVINCTRPNNNTRRRL

**Epitope name** Peptide 27

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6

*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2k, H2-d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in only 1/10 BALB/c mice tested, but reacted in 8/10 CBA/J mice.

**HXB2 Location** gp160 (289–297)

**Author Location** gp120 (292–300 SF2)

**Epitope** NESVAINCT

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF2

*HIV component:* gp120

**Species (MHC)** human

**References** Botarelli *et al.* 1991

- A non-glycosylated form of SF2 gp120, env 2-3, was used as an immunogen – 20% of T-cell clones do not recognize the glycosylated form.

**HXB2 Location** gp160 (290–306)

**Author Location** gp120 (296–312 LAI)

**Epitope** SVVEINCTRPNNNTRKS

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** gp160 (290–314)

**Author Location** Env

**Epitope** ESVVINCTRPNNNTRRSIHIGPG

**Epitope name** HIV\_env\_DRB0101\_14

**Subtype** M

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** T-cell Elispot

**Keywords** computational epitope prediction

**References** De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 1/34 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DR B0101 sequence of this peptide was TRPNNNTRR.

**HXB2 Location** gp160 (292–310)

**Author Location** gp120 (292–310 IIIB)

**Epitope** VEINCTRPNNNTRKRIIRIQ?

**Epitope name** F1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Only 1/15 responders recognized this peptide, but it had the highest SI in the study of 9.9.

**HXB2 Location** gp160 (296–307)

**Author Location** gp120 (301–324 RF)

**Epitope** CTRPNNNTRKSI

**Immunogen** HIV-1 infection

**Species (MHC)**

**Keywords** epitope processing

**References** de Lorimier *et al.* 1994

- Proton NMR spectroscopy was employed to analyze the solution conformation of a hybrid peptide, T1-SPI0RF, in order to better understand the immunogenicity of its' T helper (KQI-INMWQEVGKAMYA, CTRPNNNTRKSI), CTL (SITKGP-GRVIYATG) and B-cell epitopes (RKSITKGPGRVIYATG).
- This epitope embedded in the T1-SPI0RF peptide does not form a helical amphipathic conformation. It lacks random-coil conformations, and this may make a peptide less susceptible to complete proteolytic degradation and be favored within epitopes.

**HXB2 Location** gp160 (296–314)

**Author Location** gp120 (303–321 IIIB)

**Epitope** CTRPNNNTRKSIRIQRGPG(Y)

**Immunogen** vaccine

**Vector/Type:** peptide **Strain:** B clade IIIB

**Species (MHC)** goat

**References** Palker *et al.* 1989

- Goats were immunized with peptides containing V3 type-specific neutralizing determinants coupled to T1.

**HXB2 Location** gp160 (297–321)

**Author Location** gp120 (302–324 MN)

**Epitope** TRPNYNKRKRIHIGPGRAFYTTK

**Immunogen** vaccine

**Vector/Type:** peptide **Strain:** B clade MN

**HIV component:** V3

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Oscherwitz *et al.* 1999b

- Epitope presented as a tandem repeat (eight copies) elicits stronger B-cell and T-cell responses than the epitope presented as a single copy.
- This study indicates that the increased response was not due to neodeterminants created at the junction of the peptides, but rather due to an epitope density effect, increased immunogenicity through a high ratio of epitope to protein.

**HXB2 Location** gp160 (297–330)

**Author Location** Env (303–335 BX08)

**Epitope** TRPNNNTRKSIHIGPGRAFYATGEIIGDIRQAH

**Immunogen** vaccine

**Vector/Type:** lipopeptide

**Species (MHC)** human

**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 6/10 reacted to this peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual – this peptide was particularly immunogenic, eliciting a CTL response in five vaccinees.
- None of the 12 tested had an IgG response to gp120 or gp160 and vaccinees could be differentiated from HIV-1 seropositive individuals with a commercial HIV detection kit – no neutralizing antibodies were observed.

**HXB2 Location** gp160 (298–307)

**Author Location** Env (UG92005)

**Epitope** RPYNNTRKGI

**Immunogen** vaccine

**Vector/Type:** DNA, protein, vaccinia

**Strain:** B clade 1007, D clade UG92005

**HIV component:** gp140 **Adjuvant:** Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)

**Keywords** subtype comparisons, epitope processing, TCR usage

**References** Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by a hybridoma with V $\beta$  usage not determined.



- The epitope described here is the region of overlap of two 15mers that were both able to stimulate IL-2 production from the hybridoma (TINCTRPYNNTRKGI and RPYNNTRKGI-HIGPG)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promotor, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (298–319)

**Author Location** gp120 (300–319 89.6)

**Epitope** RPNNTRRRLSIGPGRFYA

**Epitope name** Peptide 28

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6

*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2k, H2-d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in 7/10 BALB/c mice tested, and in 5/10 CBA/J mice.

**HXB2 Location** gp160 (301–325)

**Author Location** gp120 (IIIB)

**Epitope** NNTRKSIRIQRGPGRAFVTIGKIGN

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade IIIB

*HIV component:* Env, Rev *Adjuvant:* QS21

**Species (MHC)** mouse

**Keywords** Th1

**References** Sasaki *et al.* 1998

- The env response is what is being sought, but co-expression of rev is required.
- Intramuscular versus nasal vaccination with DNA vaccine with a QS-21 adjuvant was studied.
- QS-21 enhanced the IgG2a response mediated via Th1 cytokines IFN-γ and IL-2 and delayed type hypersensitivity (DTH) in response to the V3 peptide was measured by a foot pad swelling test Sasaki *et al.* [1998]

**HXB2 Location** gp160 (302–315)

**Author Location** gp120 (307–322 IIIB)

**Epitope** NTRKSIRIQRGPGGR

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

*HIV component:* V3

**Species (MHC)** mouse

**References** Goodman-Snitkoff *et al.* 1990

- Identification of putative Th epitopes that can stimulate an antibody response in peptide-immunized mice.

**HXB2 Location** gp160 (302–321)

**Author Location** gp120 (302–321 IIIB)

**Epitope** NTRKRIRIQRGPGRAFVTIG?

**Epitope name** F2

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 5.6.

**HXB2 Location** gp160 (302–327)

**Author Location** gp120 (307–332 MN)

**Epitope** NKRKRIRIQRGPGRAFVTIKNIIGTIR

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade MN

*HIV component:* V3 *Adjuvant:* Montanide (ISA 51)

**Species (MHC)** mouse

**References** Anderson *et al.* 2001

- Hypervariable epitope constructs (HECs) are degenerative peptide cocktails that are made in a single peptide synthesis reaction. Vaccination with a V3 degenerative peptide cocktail containing 64 distinct peptides, NTRK-[SR]-I-[HR]-IGPG-[RQ]-AFY-[AT]-TG-[DE]-IG-[DN]-IRQ, elicited broader and more durable Th responses than the MN V3 peptide alone in BALB/c mice immunized and boosted with V3 peptides, although the MN peptide elicited a transient MN-specific V3 response.

**HXB2 Location** gp160 (305–321)  
**Author Location** gp120 (312–329)  
**Epitope** (CG)KSIRIQRGPGRFVTIG  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Adams *et al.* 1997

- Used as positive control in study examining T-cell response to four p24 Gag peptides.

**HXB2 Location** gp160 (308–319)  
**Author Location** gp120 (subtype C)  
**Epitope** (CKR)KIHIGPGQAFYT  
**Subtype** C  
**Immunogen** HIV-1 infection  
**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)  
**Keywords** Th1  
**References** Ahluwalia *et al.* 1997

- A V3 loop peptide modified to resemble an Indian form (GPGQ) was incorporated into ISCOMS (immune stimulating complexes) or liposomes, and used to immunize mice – the IgG2a/IgG2b Ab response was enhanced by the presentation in the ISCOM suggestive of a Th1 response.

**HXB2 Location** gp160 (308–321)  
**Author Location** gp120 (MN)  
**Epitope** RIHIGPGRFYTTK  
**Epitope name** SP10  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade MN  
*HIV component:* V3

- Species (MHC)** mouse (H-2<sup>d</sup>)  
**References** Klinman *et al.* 1995
- Hybrid T1-V3 peptide activates IL-4 and IL-6 in a dose dependent manner.
  - 10-mer from V3 contributes to this response.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (315–329 IIIB)  
**Epitope** RIQRGPGRFVTIGK  
**Epitope name** P18  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DR)  
**References** Baier *et al.* 1995

- Linked HIV-1 T1 and P18 peptides to anti-HLA-DR and IgD Fab fragments to enhance uptake by antigen presenting cells thus increase immunogenicity.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (315–329 IIIB)  
**Epitope** RIQRGPGRFVTIGK

**Epitope name** P18  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* gp160

- Species (MHC)** mouse (H-2 A<sup>d</sup>)  
**References** Takahashi *et al.* 1990
- Induces both class II restricted CD4+ Th cells, and class I restricted CD8+ CTL.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (315–329 IIIB)  
**Epitope** RIQRGPGRFVTIGK

**Epitope name** P18  
**Immunogen** peptide-HLA interaction  
**Species (MHC)** mouse (H-2 I-A<sup>d</sup>)  
**References** Takeshita *et al.* 1995

- Binds Class II H-2 I-A<sup>d</sup> requiring riqrgPgRaFvti, and Class I H-2 D<sup>d</sup>, requiring iGPgRaFvtI.

**HXB2 Location** gp160 (308–322)  
**Author Location** Env (IIIB)  
**Epitope** RIQRGPRAFVTIGK

**Epitope name** P18  
**Immunogen** vaccine  
*Vector/Type:* DNA with CMV promotor  
*Strain:* B clade IIIB *HIV component:* gp160, Rev  
*Adjuvant:* MIP-1α

- Species (MHC)** mouse (H-2<sup>d</sup>)  
**Keywords** Th1  
**References** Lu *et al.* 1999
- MIP-1α expression plasmid co-inoculated with a DNA vaccine consisting of HIV-1 pCMV160IIIB and pcREV enhanced the HIV-specific T-cell immune response as measured by a CTL test against using V3 peptide pulsed targets, and a DTH test to V3 peptide.
  - The IgG1/IgG2a response was lowered with co-inoculation of MIP-1 alpha, suggesting it preferentially elicits a Th1 response.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (308–322 IIIB)  
**Epitope** RIHIGPGRFYTTKN

**Immunogen**  
**Species (MHC)** human  
**References** Furci *et al.* 1997

- 9/11 exposed-uninfected individuals in this study had a proliferative response to a C5 peptide, but only 1/11 exposed-uninfected individuals recognized this peptide.
- 1/18 unexposed-uninfected controls could recognize this peptide.
- Erroneously documented as IIIB sequence - most likely MN peptide.

**HXB2 Location** gp160 (308–322)  
**Author Location** gp120 (315–329 IIIB)  
**Epitope** RIQRGPGRFVTIGK

**Epitope name** P18  
**Immunogen** vaccine  
*Vector/Type:* peptide  
**Species (MHC)** macaque

**References** Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Despite the proliferative response to this peptide in mice and humans, no response was observed in 3 rhesus monkeys.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** responses in children, Th1, Th2**References** Wasik *et al.* 1997

- The breadth and intensity of the CTL response and the type of Th response was studied in seven rapidly progressing HIV-1 + infants.
- IL-2 and  $\gamma$  IFN production from Th1 cells correlated with the CTLp frequency against HIV-1 Gag, Env, Nef and Pol.
- IL-4 production from Th2 cells was inversely correlated with the CTLp frequency.
- The HIV-1 + children with strong CTL responses had levels of anti-CD3 MAb induction of Th1 cells comparable to uninfected children.
- The children that did not mount a good CTL response had dramatically decreased numbers of Th1 relative to Th2 cells.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** responses in children, kinetics, Th1**References** Wasik *et al.* 2000

- Th responses measured by IL-2 responses to P18 and T1 in HIV-1 infected infants were undetectable at less than 1 month of age, and remained low in children with AIDS symptoms, but increased with age in children with slowly progressive disease.
- The kinetics and intensity of the CTL activity during the first year of life was related to the child's ability to make Th1 responses.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen****Species (MHC)** human**References** Pinto *et al.* 1995

- CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 MN)**Epitope** RIHIGPGRAFYTTKN**Epitope name** P18**Immunogen****Species (MHC)** human**References** Pinto *et al.* 1995

- CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen** HIV-1 infection**Species (MHC)** human**References** Clerici *et al.* 1989

- IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen** HIV-1 infection**Species (MHC)** human**References** Clerici *et al.* 1991a

- Peptides stimulate Th cell function and CTL activity in similar patient populations.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160**Species (MHC)** human**References** Clerici *et al.* 1991b

- Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen****Species (MHC)** human**References** Clerici *et al.* 1992

- Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen** HIV-1 infection**Species (MHC)** human**References** Clerici *et al.* 1997

- used in a study of the influence of pentoxifylline on HIV specific T-cells.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (MN)**Epitope** RIHIGPGRAFYTTKN**Immunogen****Species (MHC)** human

**References** Clerici *et al.* 1992

- Epitope P18 MN: Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men.

**HXB2 Location** gp160 (308–322)**Author Location** gp160 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human**Keywords** immunodominance**References** Wasik *et al.* 1999

- IL-2 responses associated with beta-chemokine expression were detectable at birth in the majority of uninfected infants born to HIV+ mothers, declining by age 6 months.
- In both uninfected and infected infants of HIV-positive mothers, responses to the T1 peptide (KQIINMWQEVGKAMYA) were more frequent than responses to P18.
- T1 is a highly conserved epitope, whereas P18 has a higher mutation rate due to its location in the immunodominant V3 loop region.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen** HIV-1 infection**Species (MHC)** human**References** Kaul *et al.* 1999

- Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- Helper epitopes used in this study were noted to be previously described Clerici *et al.* [1989], and were not explicitly described in Kaul *et al.* [1999]

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human**Keywords** subtype comparisons, responses in children, mother-to-infant transmission**References** Kuhn *et al.* 2001a

- In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4.
- The mothers were predominantly infected with subtype C, but the T help response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents.
- 3/33 infants with cord blood T help responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected. 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before

delivery, and 8/47 contracted HIV intrapartum or via breast-feeding.

- Measurable HIV specific T help responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1.

**HXB2 Location** gp160 (308–322)**Author Location** gp120 (315–329 MN)**Epitope** RIHIGPGRAFYTTKN**Epitope name** P18**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human**Keywords** subtype comparisons, responses in children, mother-to-infant transmission**References** Kuhn *et al.* 2001a

- In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4.
- The mothers were predominantly infected with subtype C, but the T help response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents.
- 3/33 infants with cord blood T help responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected. 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breast-feeding.
- Measurable HIV specific T help responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1.

**HXB2 Location** gp160 (308–322)**Author Location** Env (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18IIIB**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)****Assay type** Cytokine production**Keywords** mother-to-infant transmission**References** Clerici *et al.* 1993a

- Cord blood samples in 8/23 infants with HIV+ mothers showed IL-2 production in response to peptides from HIV-1 gp1260, demonstrating that Th cell priming to HIV env determinants can occur in utero. HIV-specific Th immunity in utero may be protective, as none of the 8 with HIV-1 specific Th activity became infected, while 3/15 infants with no detectable Th activated were infected.
- PBL from 10/21 of the mother showed HIV-1 specific Th activity through IL-2 production in response to Env peptides.

**HXB2 Location** gp160 (308–322)**Author Location** Env (MN)**Epitope** RIHIGPGRAFYTTKN**Epitope name** P18MN**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)****Assay type** Cytokine production**Keywords** mother-to-infant transmission**References** Clerici *et al.* 1993a

- Cord blood samples in 8/23 infants with HIV+ mothers showed IL-2 production in response to peptides from HIV-1 gp1260, demonstrating that Th cell priming to HIV env determinants can occur in utero. HIV-specific Th immunity in utero may be protective, as none of the 8 with HIV-1 specific Th activity became infected, while 3/15 infants with no detectable Th activated were infected.
- PBL from 10/21 of the mother showed HIV-1 specific Th activity through IL-2 production in response to Env peptides.

**HXB2 Location** gp160 (308–322)**Author Location** Env (IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18IIIB**Subtype** B**Immunogen** HIV-1 exposed seronegative**Species (MHC)****Assay type** Cytokine production**References** Clerici *et al.* 1994a

- Six of eight HIV-exposed health care workers had transient HIV-specific T-helper responses after percutaneous exposure to HIV, responding to two or more Env peptides among the set T1, T2, Th4.1, P18IIIB and P18MN. Responses were lost after 12–56 weeks. The HIV-specific Th responses occurred without seroconversion or PCR evidence for infection.
- Six of the eight HIV-exposed individuals responded to two or more peptides, whereas, only one individual exposed to HIV-negative blood responded to one peptide.

**HXB2 Location** gp160 (308–322)**Author Location** Env (MN)**Epitope** RIHIGPGRAFYTCKN**Epitope name** P18MN**Subtype** B**Immunogen** HIV-1 exposed seronegative**Species (MHC)****Assay type** Cytokine production**References** Clerici *et al.* 1994a

- Six of eight HIV-exposed health care workers had transient HIV-specific T-helper responses after percutaneous exposure to HIV, responding to two or more Env peptides among the set T1, T2, Th4.1, P18IIIB and P18MN. Responses were lost after 12–56 weeks. The HIV-specific Th responses occurred without seroconversion or PCR evidence for infection.
- Six of the eight HIV-exposed individuals responded to two or more peptides, whereas, only one individual exposed to HIV-negative blood responded to one peptide.

**HXB2 Location** gp160 (308–322)**Author Location** HIV-1 (IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18IIIB**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)****Assay type** Cytokine production**References** Clerici *et al.* 1994b

- IL-10-specific mRNA was upregulated in PBMC from asymptomatic, HIV-infected (HIV+) patients, and was particularly high in those with severely compromised Th cells function. Th response to HIV peptides *in vitro* could be restored by IL-10 Ab.

**HXB2 Location** gp160 (308–322)**Author Location** HIV-1 (MN)**Epitope** RIHIGPGRAFYTCKN**Epitope name** P18MN**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)****Assay type** Cytokine production**References** Clerici *et al.* 1994b

- IL-10-specific mRNA was upregulated in PBMC from asymptomatic, HIV-infected (HIV+) patients, and was particularly high in those with severely compromised Th cells function. Th response to HIV peptides *in vitro* could be restored by IL-10 Ab.

**HXB2 Location** gp160 (308–322)**Author Location** Env (315–329)**Epitope** RIHIGPGRAFYTCKN**Epitope name** P18 MN**Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** Cytokine production**Keywords** mother-to-infant transmission**References** Kuhn *et al.* 2001b

- The proliferative responses in cord blood at delivery to a cocktail of HIV Envelope peptides were infrequent (1/41) among infants whose HIV-positive mothers received antiretroviral prophylaxis at delivery to prevent transmission. Responses were 10 times more frequent among infants of HIV-seropositive women who had no antiretroviral treatment (7/29). Reductions of HIV-specific responses occurred despite persistence of detectable HIV RNA in the mothers at delivery.
- The reduction of Th responses in newborns raises the possibility that anti-retroviral exposure during pregnancy may block subsequent immune protection. The authors point two relevant citations that showed ARV exposed infants had a more rapid course of progression (Kuhn *et al.*, JID 182:104 (2000)), but were at no greater risk of infection due to subsequent breast feeding (Ditraine *et al.*, Lancet 354:2050 (1999)).

**HXB2 Location** gp160 (308–322)**Author Location** Env (315–329 IIIB)**Epitope** RIQRGPGRAFVTIGK**Epitope name** P18 IIB**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** proliferation**Keywords** responses in children, mother-to-infant transmission**References** Kuhn *et al.* 2001b

- T helper proliferative responses in cord blood at delivery to a cocktail of HIV envelope peptides were infrequent (1/41) among infants whose HIV-positive mothers received antiretroviral prophylaxis at delivery to prevent transmission. Responses were 10 times more frequent among infants of HIV-seropositive women who had no antiretroviral treatment (7/29). Reductions of HIV-specific responses occurred despite persistence of detectable HIV RNA in the mothers at delivery.
- The reduction of Th responses in newborns raises the possibility that anti-retroviral exposure during pregnancy may block subsequent immune protection. The authors point two relevant citations that showed ARV exposed infants had a more rapid course of progression (Kuhn *et al.*, JID 182:104 (2000)), but were at no greater risk of infection due to subsequent breast feeding (Ditrame *et al.*, Lancet 354:2050 (1999)).

**HXB2 Location** gp160 (308–322)

**Author Location** Env (gp160) (317–331 MN)

**Epitope** RIHIGPGRAFYTTKN

**Epitope name** P18

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** South Africa

**Assay type** proliferation

**Keywords** responses in children, variant cross-recognition or cross-neutralization

**References** Meddows-Taylor *et al.* 2004

- Viral isolates (gp160) from 16 vertically HIV-1 infected children (8 T-helper cell Env responders and 8 non-responders) were analyzed for variation after comparison with Env peptide sequences (conserved regions T1, T2 and TH4.1, hyper-variable regions P18 MN and P181 IIIB) used for *in vitro* stimulation.
- No correlation between the age, clinical category (mild or severe), HIV-1 viral load and the degree of epitope variation was established.

**HXB2 Location** gp160 (308–322)

**Author Location** Env (gp160) (317–331 IIIB)

**Epitope** RIQRGPGRAFVTIGK

**Epitope name** P18

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** South Africa

**Assay type** proliferation

**Keywords** responses in children

**References** Meddows-Taylor *et al.* 2004

- Viral isolates (gp160) from 16 vertically HIV-1 infected children (8 T-helper cell Env responders and 8 non-responders) were analyzed for variation after comparison with Env peptide sequences (conserved regions T1, T2 and TH4.1, hyper-variable regions P18 MN and P181 IIIB) used for *in vitro* stimulation.
- No correlation between the age, clinical category (mild or severe), HIV-1 viral load and the degree of epitope variation was established.

**HXB2 Location** gp160 (308–327)

**Author Location** gp120 (306–325 MN)

**Epitope** RIHIGPGRAFYTTKNIIGIT

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0101)

**References** Hayball *et al.* 1997

- Tandem repeated presentation of epitope enhances binding to class II molecule and therefore induction of T-cell proliferation.
- Tandem peptides are thought to enhance proliferation through improved recruiting of CD4 to the activation complex, which can counter-balance gp120's sequestering of CD4 and consequential inhibition of a proliferative response.

**HXB2 Location** gp160 (309–323)

**Author Location** gp120 (309–323 IIIB, B10)

**Epitope** EQRGPGRAFVTIGKI

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (309–325)

**Author Location** gp120 (314–330)

**Epitope** IQRGPGRAFVTIGKIGN

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression

**References** Caruso *et al.* 1997

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71.
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost.
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24.

**HXB2 Location** gp160 (310–328)

**Author Location** gp120 (310–329 89.6)

**Epitope** SIGPGRAFYARRNIIGDIRQ

**Epitope name** Peptide 29

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6

*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2k, H2-d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences

Th antigen processing and the frequency of immunogenic sequences.

- This peptide was reactive in 2/10 BALB/c mice tested, and in 8/10 CBA/J mice.

**HXB2 Location** gp160 (311–319)

**Author Location**

**Epitope** RGPGRFVTV

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade BH10

*HIV component:* gp120 *Adjuvant:* GM-CSF

**Species (MHC)** mouse

**References** Barouch *et al.* 2002

- gp120 encoding DNA co-injected with a plasmid carrying GMCSF gave meager CD4+ T-cell responses in BALB/c mice relative to bicistronic gp120 and GMCSF cloned into the same vector and expressed from the same promoter.
- The bicistronic gp120/GM-CSF vaccine induced an approximately 10-fold increase of CD4+ T cell proliferative responses to gp120, as well as a significant increase in IL-2, IL-4, IL-10, IFN- $\gamma$  and GM-CSF production, compared to immunization with the monocistronic pVII-gp120 with GMCSF. The enhanced proliferative responses were substantiated by CD4+ T-cell Elispot.
- Both mono and bicistronic DNA vaccines induced similar CTL responses directed against the H-2Dd restricted P18 peptide RGPRAFTVTI in murine splenocytes despite the enhanced proliferative responses.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (IIIB)

**Epitope** RGPGRFVTVI

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promoter

*Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* IL-2

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** Th1

**References** Xin *et al.* 1998

- Intranasal immunization with IL-2 expression plasmid in addition to DNA vaccine amplifies cellular response to antigen, probably via activation of Th type 1 (Th1) cells.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (IIIB)

**Epitope** RGPGRFVTVI

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promoter

*Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* IL-15

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** Th1

**References** Xin *et al.* 1999

- Intranasal immunization with IL-15 expression plasmid in addition to DNA vaccine increases DTH response and CTL activity to the antigen, and decreases the serum IgG1 to IgG2a ratio, enhancing Th type 1 (Th1) cell-mediated immunity.

- Expression of IL-2 or IL-15 can enhance Th1 response to the vaccine, but they do not appear to elicit a synergistic response.

**HXB2 Location** gp160 (311–320)

**Author Location** gp120 (IIIB)

**Epitope** RGPGRFVTVI

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promoter

*Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* CD40

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** Th1, Th2

**References** Ihata *et al.* 1999

- CD40L expression increases DTH, and Th1-dependent responses based on enhanced IgG2a titers, with no lowering of IgG1 titers.
- Elispot assay indicated co-injection with hCD40L resulted in greater numbers of IFN- $\gamma$  producing Th1 cells, as well as increased IL-4 producing Th2 cells.
- Results suggest hCD40L enhance both Th1 and Th2 cells, and such a pattern of induction is unique among adjuvants, as most adjuvants increase either Th1 or Th2.

**HXB2 Location** gp160 (311–322)

**Author Location** Env (IIIB)

**Epitope** RGPGRFVTVIGK

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promoter

*Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* GM-CSF

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** Th1, Th2

**References** Kusakabe *et al.* 2000

- The timing of delivery of the pGM-CSF expression plasmid for intramuscular DNA pCMV160IIIB/REV vaccination impacts the Th response, maximizing Th2 responses when administered 3 days prior to the DNA vaccine, and Th1 responses when administered 3 days after the DNA vaccine.

**HXB2 Location** gp160 (314–328)

**Author Location** gp120 (314–328 IIIB, B10)

**Epitope** GRAFVTVIGKIGNMRQ

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (314–341)

**Author Location** gp120 (319–346 NL43)

**Epitope** GRAFVTVIGKIGNMRQAHCNISRAKWNAT

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade NL43

*HIV component:* gp120, gp160

**Species (MHC)** human

**References** Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.

- More than 25% of vaccinees had a stimulation index of greater than 5 to this peptide.

**HXB2 Location** gp160 (315–328)

**Author Location** Env (UG92005)

**Epitope** RAYTTNIVGNIRQ

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)

**Keywords** subtype comparisons, epitope processing, TCR usage

**References** Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by two hybridomas with V $\beta$  usage not determined, but one used V $\alpha$  8.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3–4 weeks later boosted with VV, and 3–4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (317–331)

**Author Location** gp120 (324–338 IIIB)

**Epitope** FVTIGKIGNMRQAHC

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>)

**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (317–331)

**Author Location** gp160 (324–338 IIIB)

**Epitope** FVTIGKIGNMRQAHC

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>)

**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- B10.BR (H-2A<sup>k</sup>, E<sup>k</sup>) and B10.D2 (H-2A<sup>d</sup>, E<sup>d</sup>) mice immunized with rec gp160 showed a proliferative response to this peptide.
- FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL encompasses several murine Th epitopes including FVTIGKIGNMRQAHC and is referred to as a "multideterminant region" or cluster peptide.

**HXB2 Location** gp160 (317–336)

**Author Location** gp120 (321–340 MN)

**Epitope** YTTKNIIGTIRQAHCNSRA

**Epitope name** 1987

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, protein *Strain:* B clade MN  
*HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** guinea pig

**Keywords** vaccine-specific epitope characteristics, Th1

**References** Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensitivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensitivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 4/5 animals vaccinated with rec gp120 responded by DTH to this peptide, as did 4/6 vaccinated with plasmid gp120 DNA.

**HXB2 Location** gp160 (317–349)

**Author Location** gp160 (324–356 IIIB)

**Epitope** FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** human, mouse (H-2<sup>d</sup>, H-2<sup>k</sup>)

**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.



- This cluster peptide elicited proliferative responses in cells from B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>) and B10.D2 mice (H-2A<sup>d</sup>, E<sup>d</sup>), but shorter peptides from within this region stimulated H-2<sup>k</sup>, H-2<sup>d</sup>, H-2<sup>b</sup> and H-2<sup>s</sup> responses.
- IL-2 production in response to this peptide was observed in 58% (21/36) of asymptomatic HIV-infected individuals.

**HXB2 Location** gp160 (319–338)  
**Author Location** gp120 (320–339 89.6)  
**Epitope** RRNIIGDIRQAHCNISRAKW  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

- Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>)  
**Keywords** immunodominance  
**References** Dai *et al.* 2001
- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2<sup>k</sup> and BALB/c H-2<sup>d</sup> mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
  - This peptide was recognized by 7/10 CBA/J and 7/10 BALB/c mice with SI > 4, averaging 6.3 and 4.8, and is considered to be promiscuously immunodominant.
  - Uniquely immunodominant sequences tended to be in the inner domain of the protein.

**HXB2 Location** gp160 (319–338)  
**Author Location** gp120 (320–339 89.6)  
**Epitope** RRNIIGDIRQAHCNISRAKW  
**Epitope name** Peptide 30  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

- Species (MHC)** mouse  
**Donor MHC** H-2k, H2-d  
**Keywords** epitope processing, immunodominance  
**References** Dai *et al.* 2001
- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
  - This peptide was highly reactive in 7/10 BALB/c mice tested, and in 7/10 CBA/J mice and was considered one of the 3 immunodominant peptides identified that were shared in both mouse strains: RRNIIGDIRQAHCNISRAKW, NNTLQQIVIKLREKFRNKTI, GTNGTEGNDIITLQCRIKQI.

**HXB2 Location** gp160 (321–336)  
**Author Location** gp120 (IIIB)  
**Epitope** RIIGDIRKAHCNISRY  
**Immunogen** in vitro stimulation or selection

- Species (MHC)** human  
**References** Manca *et al.* 1995b
- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
  - Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (322–336)  
**Author Location** Env (1007)  
**Epitope** IIGDIRQAHCNISRE  
**Immunogen** vaccine  
*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

- Species (MHC)** mouse (H-2 IA<sup>b</sup>)  
**Keywords** subtype comparisons, epitope processing, TCR usage  
**References** Surman *et al.* 2001

- This epitope is located in the V3 region of 1007 (US, clade B) and was recognized by three hybridomas with Vβ usage Vβ 6 and not determined.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and Vβ usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (322–336)  
**Author Location** Env (UG92005)  
**Epitope** IVGNIRQAHCNVSKA  
**Immunogen** vaccine  
*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)

**Keywords** subtype comparisons, epitope processing, TCR usage

**References** Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by three hybridomas with V $\beta$  usage V $\beta$  6, 8.1, and not determined.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (322–336)

**Author Location** Env (UG92005)

**Epitope** IVGNIRQAHCNVSKA

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia

*Strain:* B clade 1007, D clade UG92005

*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)

**Keywords** subtype comparisons, epitope processing, TCR usage

**References** Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by three hybridomas with V $\beta$  usage V $\beta$  6, 8.1, and not determined.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.

- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (322–341)

**Author Location** gp120 (322–341 IIIB)

**Epitope** KIGNMRQAHCNISRAKWNT?

**Epitope name** F4

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 7.6.

**HXB2 Location** gp160 (324–336)

**Author Location** Env (UG92005)

**Epitope** GNIRQAHCNVSKA

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia

*Strain:* B clade 1007, D clade UG92005

*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)

**Keywords** subtype comparisons, epitope processing, TCR usage

**References** Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by two hybridoma with V $\beta$  usage V $\beta$ 8.2 and not determined.

- The epitope described here is the region of overlap of two 15mers that were both able to stimulate IL-2 production from the hybridoma (IVGNIRQAHCNVSKA and GNIRQAHCNVSKAKW)
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (324–338)

**Author Location** Env (UG92005)

**Epitope** GNIRQAHCNVSKAKW

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)

**Keywords** subtype comparisons, epitope processing, TCR usage

**References** Surman *et al.* 2001

- This epitope is located in the V3 region of UG92005 (UG, clade D) and was recognized by eleven hybridomas with V $\beta$  usage V $\beta$ 5, 7, 8.1, 8.2, 11 and not determined – a V $\beta$  8.1's and V $\beta$  8.2 also were shown to use V $\alpha$  8, and one of the ND used V $\alpha$  2.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the

pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.

- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (324–338)

**Author Location** gp120 (V3)

**Epitope** GNIRQAHCNVSKAKW

**Subtype** B, D

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H2b)

**Assay type** Cytokine production, CD4 T-cell Elispot - IFN $\gamma$

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Zhan *et al.* 2004

- To develop a polyvalent Env vaccine, subtype specific B and D T-helper epitopes were identified, and mixtures of strain 1007, clade B, or UG92005, clade D envelopes were given to C57BL/6J mice. Mice were intramuscularly immunized with recombinant DNA, then intraperitoneally with rVV and finally with env protein in CFA. A dilution of 1/100 could still elicit type specific responses, and responses persisted with different prime boost combinations.
- Priming with 1007 and UG92005 env's induced both Env-specific (SNNTVGNPIILPCRI and AMYAPPIAGLIQCSS) and cross-reactive (PKVSFEPPIHYCAP, C2, GNIRQAHCNVSKAKW, V3-C3) Th responses in murine spleen cells.

**HXB2 Location** gp160 (327–341)

**Author Location** gp120 (327–341 HXB2)

**Epitope** RQAHCNISRAKWNTT

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* gp120

**Species (MHC)** mouse (I-A<sup>d</sup>)

**References** Warren & Thomas 1992

- Minimum epitope and MHC restriction determined for CTL clone that recognizes the N-terminal flank of the V3 loop.

**HXB2 Location** gp160 (327–346)  
**Author Location** gp120 (331–350 MN)  
**Epitope** RQAHCNISRAKWNILRQIV  
**Epitope name** 1988  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** guinea pig  
**Keywords** vaccine-specific epitope characteristics, Th1  
**References** Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensitivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensitivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 4/5 animals vaccinated with rec gp120 responded by DTH to this peptide, and 2/6 responded that were vaccinated with plasmid gp120 DNA.

**HXB2 Location** gp160 (330–350)  
**Author Location** gp120 (330–349 IIIB)  
**Epitope** HCNISRAKWNNTLKQIASKLR?  
**Epitope name** F5  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 5.5.

**HXB2 Location** gp160 (331–345)  
**Author Location** gp120 (IIIB)  
**Epitope** CNISRAQWNNTLEQI  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (332–354)  
**Author Location** gp120 (337–359 NL43)  
**Epitope** NISRAKWNATLKQIASKLREQFG  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* gp120, gp160  
**Species (MHC)** human  
**References** Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- More than 30% of vaccinees had a stimulation index of greater than 5 to this peptide.

**HXB2 Location** gp160 (335–349)  
**Author Location** gp160 (342–356 IIIB)  
**Epitope** RAKWNNTLKQIDSKL  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)  
**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- B10.BR (H-2A<sup>k</sup>, E<sup>k</sup>), B10.A(5R) (H-2A<sup>b</sup>, E<sup>b</sup>) and B10.S(9R) (H-2A<sup>s</sup>, E<sup>s</sup>) mice immunized with rec gp160 showed a proliferative response to this peptide.
- FVTIGKIGNMRQAHCNISRAKWNNTLKQIDSKL encompasses several murine Th epitopes including RAKWNNTLKQIDSKL and is referred to as a "multideterminant region" or cluster peptide.

**HXB2 Location** gp160 (335–349)  
**Author Location** gp120 (342–356 IIIB)  
**Epitope** RAKWNNTLKQICSKL  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>i5</sup>, H-2<sup>k</sup>, H-2<sup>t4</sup>)  
**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (337–356)  
**Author Location** gp120 (341–360 MN)  
**Epitope** KWNNTLRQIVSKLKEQFKNK  
**Epitope name** 1989  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** guinea pig  
**Keywords** vaccine-specific epitope characteristics, Th1  
**References** Chattergoon *et al.* 2002

- Hartley guinea pig were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensitivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.

- A total of 7 gp120 peptides elicited a delayed type hypersensitivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 3/5 animals vaccinated with rec gp120 responded by DTH to this peptide, and 2/6 responded that were vaccinated with plasmid gp120 DNA.

**HXB2 Location** gp160 (339–359)

**Author Location** gp120 (340–359 89.6)

**Epitope** NNTLQQIVIKLREKFRNKTI

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>)

**Keywords** immunodominance

**References** Dai *et al.* 2001

- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2<sup>k</sup> and BALB/c H-2<sup>d</sup> mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.
- This peptide was recognized by 4/10 CBA/J and 6/10 BALB/c mice with SI > 4, averaging 4.9 and 5.5 and is considered to be promiscuously immunodominant.
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

**HXB2 Location** gp160 (339–359)

**Author Location** gp120 (340–359 89.6)

**Epitope** NNTLQQIVIKLREKFRNKTI

**Epitope name** Peptide 32

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2k, H2-d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in 6/10 BALB/c mice tested, and in 4/10 CBA/J mice and was considered one of the 3 immunodominant peptides identified that were shared in both mouse strains: RRNIIGDIRQAHCNISRAKW, NNTLQQIVIKLREKFRNKTI, GTNGTEGNDIITLQCRIKQI.

**HXB2 Location** gp160 (341–356)

**Author Location** gp120 (IIIB)

**Epitope** TLEQIVKKLREQFGNC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (342–361)

**Author Location** gp120 (342–361 IIIB)

**Epitope** LKQIASKLREQFGNKKTIIF?

**Epitope name** G1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 2/15 responders recognized this peptide, average SI = 6.0.

**HXB2 Location** gp160 (344–357)

**Author Location** gp120 (346–359)

**Epitope** QIVKKLREQFGNNK

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Krowka *et al.* 1990

- Conjugation of HIV peptides to liposomes and rIL-2 stimulation may enhance cell-mediated responses.

**HXB2 Location** gp160 (349–368)

**Author Location** gp120 (350–369 89.6)

**Epitope** LREKFRNKTIAFNQSSGGD

**Epitope name** Peptide 33

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2k, H2-d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.

- This peptide was reactive in 3/10 BALB/c mice tested, and in 5/10 CBA/J mice.

**HXB2 Location** gp160 (350–370)  
**Author Location** gp120 (350–370 IIIB)  
**Epitope** REQFGNNKTIIFKQSSGGDPE?  
**Epitope name** G2  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, average SI = 3.2.

**HXB2 Location** gp160 (353–360)  
**Author Location** gp120 (355–362 IIIB)  
**Epitope** FGNNKTII  
**Immunogen** SHIV infection  
**Species (MHC)** macaque  
**References** Lekutis & Letvin 1997

- C3 region minimal epitope determined through fine epitope mapping.
- Cell line was lost prior to confirmation of MHC requirements.

**HXB2 Location** gp160 (363–372)  
**Author Location** gp120 (368–377 LAI)  
**Epitope** QSSGGDPEIV  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** gp160 (364–378)  
**Author Location** gp120 (364–378 IIIB, B10)  
**Epitope** SSGGKPEIVTHSFNC  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (369–383)  
**Author Location** gp120 (369–383 IIIB, B10)  
**Epitope** PEIVTHSFNCGGEFF  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (380–393)  
**Author Location** gp120 (380–393 IIIB)  
**Epitope** GEFFYCNSTQLFNS?  
**Epitope name** G4  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** immunodominance  
**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- Five peptides were recognized most frequently: C2 (aa 142–161), C3 (aa 152–171), C5 (aa 172–191), E5 (aa 272–291) and G4 (aa 380–393). The first three were in or near V2, the other two were proximal to the V3 and V4 loops.
- 4/15 responders recognized this immunodominant peptide, average SI = 4.4.

**HXB2 Location** gp160 (381–395)  
**Author Location** gp120 (IIIB)  
**Epitope** EFFYCNTTQLFNNTW  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human  
**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (388–402)  
**Author Location** Env (388–402 HXB2)  
**Epitope** TQLFNSTWFNSTWST  
**Subtype** B

**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (DP4)  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, epitope processing, computational epitope prediction, dendritic cells  
**References** Cohen *et al.* 2006

- Motif-based quantitative matrices binding predictions, binding assays and cellular assays were used to identify 4 HLA-DP4 epitopes by scanning the whole HIV-1 genome.
- 21 peptides were predicted to bind HLA-DP4, 17 of them did bind in binding assays, 6 of them were good binders. Of the 6 good binders, 4 peptides primed peptide-specific CD4+ T cell lines restricted to HLA-DP4 molecules.

**HXB2 Location** gp160 (391–405)  
**Author Location** gp120 (IIIB)  
**Epitope** FNNTWRLNHTEGKGC  
**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (392–411)

**Author Location** gp120 (392–411 IIIIB)

**Epitope** NSTWFNSTWSTEGSNTEGS?

**Epitope name** G5

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 9.3.

**HXB2 Location** gp160 (394–408)

**Author Location** gp120 (394–408 IIIIB, B10)

**Epitope** TWFNSTWSTKGSNNT

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (399–413)

**Author Location** gp120 (399–413 IIIIB, B10)

**Epitope** TWSTKGSNNTGSDT

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (404–423)

**Author Location** gp120 (400–419 89.6)

**Epitope** GTNGTEGNDIITLQCRIKQI

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6

*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>)

**Keywords** immunodominance

**References** Dai *et al.* 2001

- Promiscuous immunodominant epitopes in gp120 were mapped by overlapping peptides in CBA/J H-2<sup>k</sup> and BALB/c H-2<sup>d</sup> mice, and all were found to be in the outer domain, proximal to regions of structural disorder indicated by the crystal structure or by sequence divergence.

- This peptide was recognized by 4/10 CBA/J and 6/10 BALB/c mice with SI > 4, averaging 4.9 and 5.5 and is considered to be promiscuously immunodominant.
- Uniquely immunodominant sequences tended to be in the inner domain of the protein.

**HXB2 Location** gp160 (404–423)

**Author Location** gp120 (400–419 89.6)

**Epitope** GTNGTEGNDIITLQCRIKQI

**Epitope name** Peptide 38

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6

*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2k, H2-d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in 8/10 BALB/c mice tested, and in 6/10 CBA/J mice, and was considered one of the 3 immunodominant peptides identified that were shared in both mouse strains: RRNIIGDIRQAHCNISRAKW, NNTLQQIVIKL-REKFRNKTI, GTNGTEGNDIITLQCRIKQI.

**HXB2 Location** gp160 (405–420)

**Author Location** Env (1007)

**Epitope** SNNTVGNPIILPCRI

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia

*Strain:* B clade 1007, D clade UG92005

*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)

**Keywords** subtype comparisons, epitope processing, TCR usage

**References** Surman *et al.* 2001

- This epitope is located in the V4C4 region of 1007 (US, clade B) and was recognized by 13 hybridomas with V $\beta$  usage V $\beta$  4, 7, 8.1, 8.2, 10, 12 and not determined – one of the V $\beta$  8.2 was shown to utilize V $\alpha$  2.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.

- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (405–420)

**Author Location** Env (gp160) (1007)

**Epitope** SNNTVGNPIILPCRI

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H2b)

**Assay type** Cytokine production, CD4 T-cell Elispot - IFN $\gamma$

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Zhan *et al.* 2004

- To develop a polyvalent Env vaccine, subtype specific B and D T-helper epitopes were identified, and mixtures of strain 1007, clade B, or UG92005, clade D envelopes were given to C57BL/6J mice. Mice were intramuscularly immunized with recombinant DNA, then intraperitoneally with rVV and finally with env protein in CFA. A dilution of 1/100 could still elicit type specific responses, and responses persisted with different prime boost combinations.
- T-cell hybridoma 1007P3-23 was isolated from mice immunized with 1007, and it recognized the peptide SNNTVGNPIILPCRI of the V4/C4 region. The minimal, core peptide recognized by 1007P3-23 was NPIIL, a sequence not found in UG92005, which has a deletion in the core, so that the equivalent region in the D isolate is NNET—ITLQCRI
- Priming mixtures of 1007 and UG92005 induced both Env-specific (SNNTVGNPIILPCRI and AMYAPPIAGLIQCSS) and cross-reactive (PKVSFEPIPIHYCAP, C2, GNIRQAHC-NVSKAKW, V3-C3) Th responses in murine spleen cells.

**HXB2 Location** gp160 (410–429)

**Author Location** gp120 (410–429 PV22)

**Epitope** GSDTITLPCRIKQFINMWQE

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR4)

**References** Callahan *et al.* 1990

- Synthetic peptides representing natural variants were used to test for recognition in the context DR4.

**HXB2 Location** gp160 (410–429)

**Author Location** gp120 (410–429 PV22)

**Epitope** GSDTITLPCRIKQFINMWQE

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR4(Dw10))

**References** Polydefkis *et al.* 1990

- Human CD4+ T-cell clones lyse recombinant vaccinia virus-infected cells that synthesize envelope gp160.

**HXB2 Location** gp160 (412–431)

**Author Location** gp120 (412–431 IIIB)

**Epitope** DTITLPCRIKQIINMWQKVG?

**Epitope name** H2

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 5.7.

**HXB2 Location** gp160 (416–431)

**Author Location** gp120 (IIIB)

**Epitope** LPCRIKQIINMWQEVY

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (418–436)

**Author Location** Env (417–435)

**Epitope** CRIKQIINMWQGVGKAMYA

**Immunogen** HIV-1 infection

**Species (MHC)** human, chimpanzee

**References** Nehete *et al.* 1998b

- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR)



**References** Baier *et al.* 1995

- Linked HIV-1 T1 and P18 peptides to anti-HLA-DR and anti-IgD Fab fragments to enhance uptake by antigen presenting cells and thus increase immunogenicity.

**HXB2 Location** gp160 (421–436)**Author Location****Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** vaccine*Vector/Type:* canarypox prime with recombinant protein boost *HIV component:* gp120**Species (MHC)** human (DRB1\*13)**Donor MHC** DRB1\*01, DRB1\*13**Assay type** proliferation**Keywords** enhancing activity, optimal epitope**References** Okazaki *et al.* 2006

- KQIINMWQEVGKAMYA-specific human CD4+ T-cell line from a healthy Caucasian American volunteer immunized with a canarypox virus vector expressing gp120 and boosted with recombinant gp120 was developed and found to be restricted to DRβ1\*13. Epitope enhancement with different amino acid substitutions was studied.
- Likely binding core for KQIINMWQEVGKAMYA was determined as WQEVGKAMY, based on single A or S substitutions that diminished recognition, and proliferation assay data using truncated peptides.
- HLA binding motif was studied using substituted peptides in anchor positions 1,4,6,9 from the N-terminus of WQEVGKAMY. In position 1, CD4+ response was reduced by kqiinm[w/ai]QEVGKAMYa substitutions, but not by kqiinm[w/f]QEVGKAMYa substitution suggesting a requirement of aromatic amino acid. In position 4, CD4 response was reduced by kqiinmMWQE[v/af]GKAMYa substitutions, but enhanced by kqiinmWQE[v/i]GKAMYa substitution, suggesting a requirement of aliphatic amino acid. In position 6, response was reduced by kqiinmWQEVG[k/ae]AMYa substitutions, but was enhanced by positively charged R substitution (kqiinmWQEVG[k/r]AMYa). In position 9, all peptides substituted with small, aromatic, or aliphatic amino acids (kqiinmWQEVGKAM[y/afi]a) induced enhanced response.
- The altered KQIINMWQE[v/i]GKAMYA peptide produced higher IFN-γ production than the original peptide, suggesting greater CD4 T-cell activation in a Th1 functional response.
- Triple substituted peptide KQIINMWQE[v/i]G[k/r]AM[y/a]A shifted the peak proliferative response to lower concentrations.

**HXB2 Location** gp160 (421–436)**Author Location** Env (421–436 IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** vaccine*Vector/Type:* peptide *Strain:* modified B clade IIIB *HIV component:* Env**Species (MHC)** mouse (Ek)**Assay type** Cytokine production, Th support of CTL response**Keywords** binding affinity, Th1**References** Ahlers *et al.* 2001

- BALB/c and A.AL were immunized with an Env-peptide vaccine construct containing the CTL epitope P18IIIB and a T helper epitope.
- Substitution of Glu (wt) to Ala, kqiinmwqAvgkamy, caused increased affinity for MHC class II Ek. This resulted in the upregulation of CD40L in the responding Th cells, and shifted the response towards Th1. Increased Th responses stimulated DCs to produce higher levels of IL-12, and B7-1 and B7-2, thus enhance CTL responses.
- The modified epitope, T1A, elicited stronger protection against increasing doses of viral challenge with vaccinia expressing HIV-1 IIIB gp120 compared to the wildtype epitope T1.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (428–443 IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** vaccine*Vector/Type:* peptide *Strain:* B clade IIIB**Species (MHC)** mouse (H-2<sup>d</sup>)**References** Klinman *et al.* 1995

- Hybrid T1-V3 peptide activates IL-4 and IL-6 in a dose dependent manner.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (428–443 IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** vaccine*Vector/Type:* peptide *Strain:* B clade IIIB**Species (MHC)** mouse (H-2<sup>k</sup>)**References** Ahlers *et al.* 1997b

- first identified Th epitope in HIV.
- Alanine at position 436 (instead of E in wild-type) enhances MHC binding and antigenicity of peptide by several orders of magnitude.
- Vaccines with a CTL epitope linked to a more potent helper epitope yielded greatly enhanced CTL response relative to the wildtype helper epitope.
- T1 peptide linked to CTL epitopes in four vaccine constructs used to immunize mice: KQIINMWQEVGKAMYAPPISGQIRRIQRGPGRAFVTIGK, KQIINMWQEVGKAMYAPPISGQIRRIQRGPGRAFVTI, KQIINMWQAVGKAMYAPPISGQIRRIQRGPGRAFVTIGK, KQIINMWQAVGKAMYAPPISGQIRRIQRGPGRAFVTI.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (428–443 IIIB, B10)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** computer prediction**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)**References** Cease *et al.* 1987

- 1 of 2 functional epitopes identified using an amphipathic helix epitope prediction algorithm.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (428–443 IIIB)**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1**Immunogen** vaccine*Strain:* B clade IIIB *HIV component:* gp160**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>l4</sup>)**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (421–436)**Author Location** gp160 (428–443 IIIB)**Epitope** KQIINMWQEVGKAMYA**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- B10.BR (H-2A<sup>k</sup>, E<sup>k</sup>), B10.D2 (H-2A<sup>d</sup>, E<sup>d</sup>) and B10.S(9R) (H-2A<sup>s</sup>, E<sup>s</sup>) mice immunized with rec gp160 showed a proliferative response to this peptide.
- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes including KQIINMWQEVGKAMYA and is referred to as a "multideterminant region" or cluster peptide.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (428–443 IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** vaccine*Vector/Type:* peptide *Strain:* B clade IIIB**Species (MHC)** mouse (H-2E $\alpha$  E $\beta$ <sup>k</sup>)**References** Boehncke *et al.* 1993

- C3H H2<sup>k</sup> mice were used for immunization in the study because H-2<sup>k</sup> mice are particularly good T1 responders – T1 can be presented by E $\alpha$  E $\beta$ <sup>k</sup> but not E $\alpha$  E $\beta$ <sup>b</sup> – the nature of the T1 class II molecular interaction was thoroughly explored.
- Alanine substitutions across peptide did not negatively affect MHC binding or effective presentation of epitope, except at three critical residues (432N, 435Q, 439K), however substitutions with larger side chains often diminished activity – only a few amino acids were found to be critical for class II interaction and for maintaining T-cell receptor specificity.
- A gain in potency was observed when 436E was replaced with A, suggesting that substitutions in positions that interfere with binding might allow the design of a more potent vaccine.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (426–441 IIIB)**Epitope** KQFINMWQEWGKAMYA**Immunogen****Species (MHC)** human**References** Furci *et al.* 1997

- Epitope T1 variant: 9/11 exposed-uninfected individuals in this study had a proliferative response to a C5 peptide, but none reacted with this previously defined epitope.
- IIIB position 435 listed as W in this epitope as opposed to V in the sequence.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (428–433 IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** responses in children, kinetics, Th1**References** Wasik *et al.* 2000

- Th responses measured by IL-2 responses to P18 and T1 in HIV-1 infected infants were undetectable at less than 1 month of age, and remained low in children with AIDS symptoms, but increased with age in children with slowly progressive disease.
- The kinetics and intensity of the CTL activity during the first year of life was related to the child's ability to make Th1 responses.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (428–433 IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** responses in children, Th1, Th2**References** Wasik *et al.* 1997

- The breadth and intensity of the CTL response and the type of Th response was studied in seven rapidly progressing HIV-1 + infants.
- IL-2 and  $\gamma$  IFN production from Th1 cells correlated with the CTLp frequency against HIV-1 Gag, Env, Nef and Pol.
- IL-4 production from Th2 cells was inversely correlated with the CTLp frequency.
- The HIV-1 + children with strong CTL responses had levels of anti-CD3 MAb induction of Th1 cells comparable to those of uninfected children.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (428–443 IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** vaccine*Vector/Type:* vaccinia *Strain:* B clade IIIB *HIV component:* gp160**Species (MHC)** human**References** Berzofsky *et al.* 1988

- Proliferative response to T1 and T2 peptides in 14 immunized, uninfected humans.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (428–443 IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** vaccine*Vector/Type:* peptide *Strain:* B clade IIIB**Species (MHC)** goat**References** Palker *et al.* 1989

- Goats immunized with peptides containing V3 type-specific neutralizing determinants coupled to T1.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Clerici *et al.* 1989

- IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Clerici *et al.* 1991a

- Peptides stimulate Th cell function and CTL activity in similar patient populations.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB

*HIV component:* gp160

**Species (MHC)** human

**References** Clerici *et al.* 1991b

- Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Immunogen**

**Species (MHC)** human

**References** Clerici *et al.* 1992

- Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Immunogen** vaccine

*Vector/Type:* bacteriophage coat protein

*Strain:* B clade MN *HIV component:* V3

**Species (MHC)** mouse

**References** di Marzo Veronese *et al.* 1994

- Epitope T1 was engineered into a filamentous bacteriophage coat protein, and the Th epitope stimulated Ab production to the V3 loop.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

**Species (MHC)** chimpanzee

**References** Haynes *et al.* 1993

- Hybrid T1-V3 peptide immunogenicity reduced when the fusogenic domain of gp41 was added.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Clerici *et al.* 1997

- Used in a study of the influence of pentoxifylline on HIV specific T-cells.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Immunogen**

**Species (MHC)** human

**References** Pinto *et al.* 1995

- CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers.

**HXB2 Location** gp160 (421–436)

**Author Location** gp160 (428–433 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)** human

**Keywords** immunodominance

**References** Wasik *et al.* 1999

- IL-2 responses associated with beta-chemokine expression were detectable at birth in the majority of uninfected infants born to HIV+ mothers, declining by age 6 months.
- T1 peptide: In both uninfected and infected infants of HIV-positive mothers, responses to the T1 peptide were more frequent than responses to P18 (RIQRGPGRAFVTIGK)
- T1 is a highly conserved epitope, whereas P18 has a higher mutation rate due to its location in the immunodominant V3 loop region.

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (428–443 IIIB)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Kaul *et al.* 1999

- Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
- Helper epitopes used in this study were noted to be previously described Clerici *et al.* [1989], and were not explicitly described in Kaul *et al.* [1999]

**HXB2 Location** gp160 (421–436)

**Author Location** gp120 (MN)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1**Immunogen** HIV-1 infection, vaccine*Vector/Type:* peptide *Strain:* B clade MN**Species (MHC)** human**References** Bartlett *et al.* 1998

- C4-V3 PV (polyvalent HIV envelope synthetic peptide immunogen) consisted of T1 helper epitope presented in tandem with a V3 loop CTL epitope from one of four different North American strains.
- This was a pilot phase I study involving vaccination of ten HIV-infected subjects who were HLA-B7-positive.
- Enhanced lymphoproliferative response to peptide was observed in 5/8 vaccinees – increase in neutralizing antibody responses in 4/8 vaccinees.

**HXB2 Location** gp160 (421–436)**Author Location** gp120**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)** human**Keywords** subtype comparisons, responses in children, mother-to-infant transmission**References** Kuhn *et al.* 2001a

- In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4.
- The mothers were predominantly infected with subtype C, but the T help response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents.
- 3/33 infants with cord blood T help responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected. 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breast-feeding.
- Measurable HIV specific T help responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1.

**HXB2 Location** gp160 (421–436)**Author Location** gp120 (428–443 RF)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** HIV-1 infection**Species (MHC)****Keywords** epitope processing**References** de Lorimier *et al.* 1994

- Proton NMR spectroscopy was employed to analyze the solution conformation of a hybrid peptide, T1-SP10RF, in order to better understand the immunogenicity of its' T helper (KQI-INMWQEVGKAMYA, CTRPNNTRKSI), CTL (SITKGP-GRVIYATG) and B-cell epitopes (RKSITKGPGRVIYATG).

- As a free peptide, the T1 segment, a T-helper epitope is in an extended conformation with nascent helical conformation. It may form a beta strand in native gp120, and a nonnative conformation may account for the inability of free T1 peptide to elicit antibody responses, in contrast to the T1 segment in native gp120. It lacks random-coil conformations, and it is suggested that this may make the peptide less susceptible to complete proteolytic degradation, and be favored within epitopes.

**HXB2 Location** gp160 (421–436)**Author Location** Env (428–443 IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Immunogen** HIV-1 infection, HIV-1 exposed seronegative**Species (MHC)****Assay type** Cytokine production**Keywords** mother-to-infant transmission**References** Clerici *et al.* 1993a

- Cord blood samples in 8/23 infants with HIV+ mothers showed IL-2 production in response to peptides from HIV-1 gp1260, demonstrating that Th cell priming to HIV env determinants can occur in utero. HIV-specific Th immunity in utero may be protective, as none of the 8 with HIV-1 specific Th activity became infected, while 3/15 infants with no detectable Th activated were infected.
- PBL from 10/21 of the mothers showed HIV-1 specific Th activity through IL-2 production in response to Env peptides.

**HXB2 Location** gp160 (421–436)**Author Location** Env (IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Subtype** B**Immunogen** HIV-1 exposed seronegative**Species (MHC)****Assay type** Cytokine production**References** Clerici *et al.* 1994a

- Six of eight HIV-exposed health care workers had transient HIV-specific T-helper responses after percutaneous exposure to HIV, responding to two or more Env peptides among the set T1, T2, Th4.1, P18IIIB and P18MN. Responses were lost after 12–56 weeks. The HIV-specific Th responses occurred without seroconversion or PCR evidence for infection.
- Six of the eight HIV-exposed individuals responded to two or more peptides, whereas, only one individual exposed to HIV-negative blood responded to one peptide.

**HXB2 Location** gp160 (421–436)**Author Location** HIV-1 (IIIB)**Epitope** KQIINMWQEVGKAMYA**Epitope name** T1**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)****Assay type** Cytokine production**References** Clerici *et al.* 1994b

- IL-10-specific mRNA was upregulated in PBMC from asymptomatic, HIV-infected (HIV+) patients, and was particularly high in those with severely compromised Th cells function. Th response to HIV peptides *in vitro* could be restored by IL-10 Ab.

**HXB2 Location** gp160 (421–436)

**Author Location** Env (428–443)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** proliferation

**Keywords** responses in children, mother-to-infant transmission

**References** Kuhn *et al.* 2001b

- T helper proliferative responses in cord blood at delivery to a cocktail of HIV envelope peptides were infrequent (1/41) among infants whose HIV-positive mothers received antiretroviral prophylaxis at delivery to prevent transmission. Responses were 10 times more frequent among infants of HIV-seropositive women who had no antiretroviral treatment (7/29). Reductions of HIV-specific responses occurred despite persistence of detectable HIV RNA in the mothers at delivery.
- The reduction of Th responses in newborns raises the possibility that anti-retroviral exposure during pregnancy may block subsequent immune protection. The authors point two relevant citations that showed ARV exposed infants had a more rapid course of progression (Kuhn *et al.*, JID 182:104 (2000)), but were at no greater risk of infection due to subsequent breast feeding (Ditrane *et al.*, Lancet 354:2050 (1999)).

**HXB2 Location** gp160 (421–436)

**Author Location** Env (gp160) (421–436)

**Epitope** KQIINMWQEVGKAMYA

**Epitope name** T1

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** South Africa

**Assay type** proliferation

**Keywords** responses in children, variant cross-recognition or cross-neutralization

**References** Meddows-Taylor *et al.* 2004

- Viral isolates (gp160) from 16 vertically HIV-1 infected children (8 T-helper cell Env responders and 8 non-responders) were analyzed for variation after comparison with Env peptide sequences (conserved regions T1, T2 and TH4.1, hyper-variable regions P18 MN and P181 IIIB) used for *in vitro* stimulation.
- No correlation between the age, clinical category (mild or severe), HIV-1 viral load and the degree of epitope variation was established.

**HXB2 Location** gp160 (421–444)

**Author Location** gp160 (428–451 IIIB)

**Epitope** KQIINMWQEVGKAMYAPPISGQIR

**Immunogen** HIV-1 infection, vaccine

**Vector/Type:** protein **Strain:** B clade IIIB  
**HIV component:** gp160 **Adjuvant:** Complete Freund's Adjuvant (CFA)

**Species (MHC)** human, mouse (H-2<sup>b</sup>, H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)

**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
- Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
- This cluster peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.D2 mice (H-2A<sup>d</sup>, E<sup>d</sup>), B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>), and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)
- IL-2 production in response to this peptide was observed in 73% (8/11) of asymptomatic HIV-infected individuals.

**HXB2 Location** gp160 (421–444)

**Author Location** gp120 (428–451 IIIB)

**Epitope** KQIINMWQEVGKAMYAPPISGQIR

**Epitope name** T1

**Immunogen** vaccine

**Vector/Type:** peptide **Strain:** B clade IIIB

**Species (MHC)** mouse (H2<sup>d</sup>)

**References** Shirai *et al.* 1996a

- Linked to a CTL epitope from hepatitis C virus, induced CD4+ helper cells producing IL-2.

**HXB2 Location** gp160 (421–444)

**Author Location** Env (gp160) (HIV-1 IIIB)

**Epitope** KQIINMWQEVGKAMYAPPISGQIR

**Immunogen** vaccine

**Vector/Type:** peptide **Strain:** B clade IIIB

**HIV component:** Env **Adjuvant:** E. coli mutant heat labile enterotoxin (LT-R72), Montanide (ISA 51)

**Species (MHC)** macaque

**Assay type** proliferation

**Keywords** mucosal immunity

**References** Belyakov *et al.* 2001

- Intrarectal vaccination with a Th and CTL peptide vaccine provided better protection against intrarectal challenge with pathogenic SHIV-Ku1 than subcutaneous administered vaccine. In some animals after the initial viremia, viral loads were diminished to undetectable levels in the blood and intestine, and CD4+ T cells were better preserved.
- The CD4 T-cell proliferative response correlated with the level of the CTL response.

**HXB2 Location** gp160 (423–440)

**Author Location** gp120 (428–445)

**Epitope** FINMWQEVGKAMYAPPIS

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression

**References** Caruso *et al.* 1997

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71.
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost.
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24.

**HXB2 Location** gp160 (424–438)  
**Author Location** gp120 (424–438 IIIB, B10)  
**Epitope** INMWQEVGKAMYAPP  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (425–439)  
**Author Location** gp160 (432–446 IIIB)  
**Epitope** NMWQEVGKAMYAPPI  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (H-2<sup>S</sup>)  
**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- B10.S(9R) (H-2A<sup>S</sup>, E<sup>S</sup>) mice immunized with rec gp160 showed a proliferative response to this peptide.
- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes including NMWQEVGKAMYAPPI and is referred to as a "multideterminant region" or cluster peptide.

**HXB2 Location** gp160 (425–439)  
**Author Location** gp120 (432–446 IIIB)  
**Epitope** NMWQEVGKAMYAPPI  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>L4</sup>)  
**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (426–441)  
**Author Location** gp120 (IIIB)  
**Epitope** MWQEVGKAMYAPPIGC  
**Immunogen** *in vitro* stimulation or selection  
**Species (MHC)** human  
**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (430–444)  
**Author Location** gp160 (437–451 IIIB)  
**Epitope** VGKAMYAPPISGQIR  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>S</sup>)  
**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.D2 mice (H-2A<sup>d</sup>, E<sup>d</sup>), B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>), and B10.S(9R) mice (H-2A<sup>S</sup>, E<sup>S</sup>)
- KQIINMWQEVGKAMYAPPISGQIR encompasses several murine Th epitopes including VGKAMYAPPISGQIR and is referred to as a "multideterminant region" or cluster peptide.

**HXB2 Location** gp160 (430–444)  
**Author Location** gp120 (437–451 IIIB)  
**Epitope** VGKAMYAPPISGQIR  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>d</sup> H-2<sup>i5</sup>, H-2<sup>k</sup>, H-2<sup>L4</sup>)  
**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (430–453)  
**Author Location** gp120 (430–453)  
**Epitope** VGKAMYAPPISGQIRCSSNITGLL  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>b</sup>)  
**Keywords** epitope processing  
**References** Sjolander *et al.* 1996

- Study demonstrates that T-cell determinants from glycoproteins can depend on the glycosylation of the protein.
- Peptide stimulation of an *in vitro* proliferative response required *in vivo* priming with glycosylated protein.
- Local glycosylation sites thought not to be part of the epitope, but may be important for epitope processing.

**HXB2 Location** gp160 (432–451)  
**Author Location** gp120 (432–451 IIIB)  
**Epitope** KAMYAPPISGQIRCSSNITG?  
**Epitope name** H4  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.

## gp160 Helper/CD4+ T-cell epitopes

- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 6.3.

**HXB2 Location** gp160 (433–447)

**Author Location** Env (UG92005)

**Epitope** AMYAPPIAGLIQCSS

**Immunogen** vaccine

*Vector/Type:* DNA, protein, vaccinia

*Strain:* B clade 1007, D clade UG92005

*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)

**Keywords** subtype comparisons, epitope processing, TCR usage

**References** Surman *et al.* 2001

- This epitope is located in the C4 region of UG92005 (UG, clade D) and was recognized by ten hybridomas with V $\beta$  usage V $\beta$  6, 8.1, 8.2, 13, 14 and not determined – among the ND V $\beta$  set, three V $\alpha$ s were identified, V $\alpha$  2, 8, and 11.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3–4 weeks later boosted with VV, and 3–4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (433–447)

**Author Location** Env (gp160) (UG92005)

**Epitope** AMYAPPIAGLIQCSS

**Subtype** D

**Immunogen** vaccine

## HIV Helper/CD4+ T-Cell Epitope Tables

*Vector/Type:* DNA, protein, vaccinia

*Strain:* B clade 1007, D clade UG92005

*HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H2b)

**Assay type** Cytokine production, CD4 T-cell Elispot - IFN $\gamma$

**Keywords** vaccine-induced epitopes, variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Zhan *et al.* 2004

- To develop a polyvalent Env vaccine, subtype specific B and D T-helper epitopes were identified, and mixtures of strain 1007, clade B, or UG92005, clade D envelopes were given to C57BL/6J mice. Mice were intramuscularly immunized with recombinant DNA, then intraperitoneally with rVV and finally with env protein in CFA. A dilution of 1/100 could still elicit type specific responses, and responses persisted with different prime boost combinations.
- T-cell hybridoma UGP2-17 was isolated from mice immunized with env sequence UG92005 (clade D), and it recognized the C4/V4 region peptide AMYAPPIAGLIQCSS. The minimal peptide recognized by 10007P3-23 was PPIAGLIQ, which matched only 5/8 residues in the B clade isolate, ppiRgQiK.
- Priming with 1007 and UG env's induced both Env-specific (SNNTVGNPIILPCRI and AMYAPPIAGLIQCSS) and cross-reactive (PKVSFEPPIHYCAP, C2, GNIRQAHC-NVSKAKW, V3-C3) Th responses in murine spleen cells.

**HXB2 Location** gp160 (436–451)

**Author Location** gp120 (IIIB)

**Epitope** APPIGGQISCSNITY

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (438–460)

**Author Location** gp120 (443–465 NL43)

**Epitope** PISGQIRCSSNITGLLLTRDGGN

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade NL43

*HIV component:* gp120, gp160

**Species (MHC)** human

**References** Sitz *et al.* 1999

- There was a great breadth of proliferative response to env peptides in 19 HIV-1 infected rgp160 and 17 HIV-1 infected rgp120 vaccine recipients.
- Close to 40% of vaccinees had a stimulation index of greater than 5 to this peptide.

**HXB2 Location** gp160 (439–448)

**Author Location** gp120 (151–160 W6.ID)

**Epitope** IGGQIRCSSN

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade W61D *HIV component:* gp120 *Adjuvant:* MPL-SE adjuvant, QS21

**Species (MHC)** human

**References** Jones *et al.* 1999

- HIV-1 specific T-cell lines isolated from an HIV seronegative volunteer vaccinated with rgp120 and a QS21/MPL adjuvant.
- One T-cell line responds to two overlapping peptides, and the region of overlap is IGGQIRCSSN.
- The IIIB version of the first reactive peptide, EVGKAMYAP-PIGGQIRCSSN, has a single substitution and induces proliferation as well as the original W61D peptide: evgkamyappiS-gqircssn.

**HXB2 Location** gp160 (439–461)

**Author Location** Env (438–460)

**Epitope** IRGQIRCSSNITGLLLTRDGGNN

**Epitope name** HIV\_env\_DRB0101\_1

**Subtype** M

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** T-cell Elispot

**Keywords** computational epitope prediction

**References** De Groot *et al.* 2004

- Bioinformatic tools (EpiMatrix and Conservatrix) were employed to predict 9 highly conserved and promiscuous class II restricted T helper epitopes from HIV-1 env sequences for a cross-clade polyepitope vaccine. 10/34 HIV-1 infected patients induced Th1 immune responses to 8/9 study peptides.
- 2/28 subjects tested responded to this peptide.
- Class II peptides containing putative epitopes were selected to favor DRB0101 presentation, as there is a transgenic mouse model for this allele for future vaccine studies. The highest scoring DRB0101 sequence within this peptide was QIRCSS-NIT.

**HXB2 Location** gp160 (446–461)

**Author Location** gp120 (IIIB)

**Epitope** SSNITGLLLTRDGGTC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (452–471)

**Author Location** gp120 (452–471 IIIB)

**Epitope** LLLTRDGGNSNNESEIFRPG?

**Epitope name** I1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.

- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.

- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.

- 2/15 responders recognized this peptide, average SI = 3.5.

**HXB2 Location** gp160 (456–470)

**Author Location** gp120 (IIIB)

**Epitope** RDGGTNVTNDTEVFR

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.

- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (459–473)

**Author Location** gp120 (459–473 IIIB, B10)

**Epitope** GNSNNESEIFRPGGG

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (468–483)

**Author Location** gp120 (466–481)

**Epitope** FRPGGGMRDNWRSEL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Krowka *et al.* 1990

- Conjugation of HIV peptides to liposomes and rIL-2 stimulation may enhance cell-mediated responses.

**HXB2 Location** gp160 (472–491)

**Author Location** gp120 (472–491 IIIB)

**Epitope** GGDMDRDNWRSELYKYKVVKI?

**Epitope name** I3

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.

- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.

- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.



- 2/15 responders recognized this peptide, average SI = 7.2.

**HXB2 Location** gp160 (474–488)  
**Author Location** gp120 (474–488 IIIB, B10)  
**Epitope** DMRDNWRSELYKYKV

- Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a
- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (476–490)  
**Author Location** gp120 (483–497 IIIB)  
**Epitope** RDNWRSELYKYKVVK  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* gp160

- Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>t4</sup>)  
**References** Hale *et al.* 1989
- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (476–490)  
**Author Location** gp160 (483–497 IIIB)  
**Epitope** RDNWRSELYKYKVVK  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

- Species (MHC)** mouse (H-2<sup>k</sup>, H-2<sup>s</sup>)  
**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in B10.BR mice (H-2A<sup>k</sup> and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)
- RDNWRSELYKYKVVKIEPLGVAPT encompasses several murine Th epitopes including RDNWRSELYKYKVVK and is referred to as a "multideterminant region" or cluster peptide.

**HXB2 Location** gp160 (476–499)  
**Author Location** gp160 (483–506 IIIB)  
**Epitope** RDNWRSELYKYKVVKIEPLGVAPT  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

- Species (MHC)** human, mouse (H-2<sup>b</sup>, H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)  
**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a
- RDNWRSELYKYKVVKIEPLGVAPT encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
  - Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
  - This cluster peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.D2 mice (H-2A<sup>d</sup>, E<sup>d</sup>), B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>), and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)

- IL-2 production in response to this peptide was observed in 52% (14/27) of asymptomatic HIV-infected individuals.

**HXB2 Location** gp160 (479–498)  
**Author Location** gp120 (481–500 MN)  
**Epitope** WRSELYKYKVVTIEPLGVAP

- Epitope name** 2013  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA, protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** guinea pig  
**Keywords** vaccine-specific epitope characteristics, Th1  
**References** Chattergoon *et al.* 2002

- Hartley guinea pigs were intradermally injected with either recombinant protein or plasmid expressed gp120 and monitored for delayed type hypersensitivity (DTH) responses after vaccination, which are related to Th1 T-cell responses. CFA did not augment responses in animals vaccinated with plasmid.
- A total of 7 gp120 peptides elicited a delayed type hypersensitivity (DTH) response after vaccination, out of a set of 60 overlapping peptides that spanned gp120. The vaccine delivery system, DNA versus rec protein, resulted in the recognition of distinct peptides.
- 0/5 animals vaccinated with rec gp120 responded by DTH to this peptide, while 6/6 vaccinated with plasmid gp120 DNA responded.

**HXB2 Location** gp160 (481–498)  
**Author Location** gp160 (481–498 clade B consensus)  
**Epitope** SELYLYKVVKIEPLGVAP  
**Subtype** B

- Immunogen** HIV-1 infection, computer prediction  
**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0405, DRB1\*0701, DRB1\*1101, DRB1\*1302, DRB1\*1501, DRB5\*0101)  
**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA  
**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While the reacting peptide was SELYLYKVVKIEPLGVAP, shorter LYLYKVVKIEPLGV was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of in vitro peptide presentation to CD4 T cells.

**HXB2 Location** gp160 (482–501)  
**Author Location** gp120 (482–501 IIIB)  
**Epitope** ELYKYKVVKIEPLGVAPTKA  
**Immunogen** vaccine

- Vector/Type:* DNA *Strain:* B clade IIIB  
*HIV component:* Env

**Species (MHC)** macaque

**References** Lekutis *et al.* 1997

- HIV-1 env DNA vaccine induced Th cell response to this epitope in a rhesus monkey.
- Epitope was recognized by both monkeys used in this study.

**HXB2 Location** gp160 (482–501)

**Author Location** gp120 (482–501 IIIB)

**Epitope** ELYKYKVVVKIEPLGVAPTKA?

**Epitope name** I4

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 3/15 responders recognized this peptide, average SI = 6.0.

**HXB2 Location** gp160 (483–502)

**Author Location** gp120 (480–499 89.6)

**Epitope** LYKYKVVRIEPIGVAPTRAK

**Epitope name** Peptide 46

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6

*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2k, H2-d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in 7/10 BALB/c mice tested, and in only 1/10 CBA/J mice.

**HXB2 Location** gp160 (484–496)

**Author Location** gp120 (484–496 HXB2)

**Epitope** YKYKVVVKIEPLGV

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade HXB2

*HIV component:* Env

**Species (MHC)** macaque (DR\*W201)

**References** Lekutis & Letvin 1998

- Variants of this epitope with substitutions at position 490(K) retained ability to bind to MHC class II, but failed to induce proliferation/cytokine secretion in HIV-1 env-specific CD4+ Th cells.
- The modified peptide antagonized the wildtype peptide-induced proliferative response.

**HXB2 Location** gp160 (484–498)

**Author Location** gp120 (484–498 IIIB, B10)

**Epitope** YKYKVVVKIEPLGVAP

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (484–499)

**Author Location** gp120 (492–506 IIIB)

**Epitope** CKYKVVVKIEPLGVAPT

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>i5</sup>, H-2<sup>k</sup>, H-2<sup>t4</sup>)

**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (485–499)

**Author Location** gp160 (492–506 IIIB)

**Epitope** KYKVVVKIEPLGVAPT

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB

*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)

**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from all H-2 haplotypes tested: B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.D2 mice (H-2A<sup>d</sup>, E<sup>d</sup>), B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>), and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)
- RDNWRSELYKYKVVVKIEPLGVAPT encompasses several murine Th epitopes including KYKVVVKIEPLGVAPT and is referred to as a "multideterminant region" or cluster peptide.

**HXB2 Location** gp160 (485–500)

**Author Location** gp120 (IIIB)

**Epitope** KYKVIKIEPLGIAPTC

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (486–494)

**Author Location** gp120 (486–494 IIIB)

**Epitope** YKVVVKIEPL

**Immunogen** SHIV infection

**Species (MHC)** macaque (DRB\*W201)

**References** Lekutis & Letvin 1997

- C5 region minimal epitope determined through fine epitope mapping.

**HXB2 Location** gp160 (487–512)

**Author Location** gp120 (494–518 IIIB)

**Epitope** KVKKIEPLGVAPTAKARRVVQREKRC

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB

**Species (MHC)** mouse

**References** Goodman-Snitkoff *et al.* 1990

- Identification of putative Th epitopes that stimulate an antibody response in peptide immunized mice.

**HXB2 Location** gp160 (492–512)

**Author Location** gp120 (492–512 IIIB)

**Epitope** EPLGVAPTAKARRVVQREKRA?

**Epitope name** I5

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 1/15 responders recognized this peptide, SI = 4.9.

**HXB2 Location** gp160 (493–511)

**Author Location** gp120 (490–508 89.6)

**Epitope** PIGVAPTRAKRRTVQREKR

**Epitope name** Peptide 47

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6

*HIV component:* gp120 *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)

**Species (MHC)** mouse

**Donor MHC** H-2k, H2-d

**Keywords** epitope processing, immunodominance

**References** Dai *et al.* 2001

- Helper T-cell proliferative responses to gp120 vaccines in 2 mouse strains, CBA/J and BALB/c, were mapped using 47 overlapping peptides that span gp120. Promiscuously immunodominant peptides were identified in both mice strains that were located in the outer domain of gp120 and were associated with regions of local structural disorder in proximal N-terminal segments, suggesting 3-D protein structure influences Th antigen processing and the frequency of immunogenic sequences.
- This peptide was reactive in only 2/10 BALB/c mice tested, and in 8/10 CBA/J mice.

**HXB2 Location** gp160 (499–511)

**Author Location** gp120 (IIIB)

**Epitope** TKAKRRVVEREKR

**Immunogen** in vitro stimulation or selection

**Species (MHC)** human (DR)

**References** Wilson *et al.* 1997b

- Thought to be a mimic of a HLA class II DR  $\beta$  chain variable region.
- Response to this epitope may cause a breakdown of self-tolerance.
- Presentation of epitope induced autoreactive T-cell lines in PBMC from uninfected donors.
- Suppression of proliferation to soluble antigens by the CD8+ fraction of TKAKRRVVEREKR stimulated T-cells was observed.

**HXB2 Location** gp160 (499–519)

**Author Location** gp41 (MN)

**Epitope** TKAKRRVVQREKRAAIGALF

**Epitope name** TF20

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** Cytokine production, proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** HAART, ART, acute/early infection

**References** Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymphoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail. These Th responses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.

**HXB2 Location** gp160 (512–534)

**Author Location**

**Epitope** AVGIGAVFLGFLGAAGSTMGAAS

**Epitope name** HIV-VAX-1060

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.

- 1/13 US test subjects responded to this 23-mer by CD4 Eli-Spot assay. The core computer-predicted peptide was FLGFLGAAG.

**HXB2 Location** gp160 (519–543)  
**Author Location** gp41 (519–543)  
**Epitope** FLGFLGAAGSTMGAASLTLTVQARC  
**Immunogen** vaccine

- Vector/Type:* peptide  
**Species (MHC)** mouse (H-2<sup>bxk</sup>, H-2<sup>sxd</sup>)  
**References** Sastry & Arlinghaus 1991
- Peptides induced T-cell proliferative response to immunizing peptide and to gp160.

**HXB2 Location** gp160 (519–543)  
**Author Location** Env (519–543)  
**Epitope** FLGFLGAAGSTMGAASLTLTVQARC  
**Immunogen** vaccine

- Vector/Type:* peptide  
**Species (MHC)** macaque  
**References** Nehete *et al.* 1993
- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice, and in rhesus monkeys.
  - Proliferative response to this peptide was observed in 3/3 immunized rhesus monkeys.

**HXB2 Location** gp160 (519–543)  
**Author Location** Env (519–543)  
**Epitope** FLGFLGAAGSTMGAASLTLTVQARC  
**Immunogen** HIV-1 infection

- Species (MHC)** human, chimpanzee  
**References** Nehete *et al.* 1998b
- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env.

**HXB2 Location** gp160 (547–561)  
**Author Location** gp41 (547–561 IIIB, B10)  
**Epitope** GIVQQNNLLRAIEA  
**Immunogen** HIV-1 infection

- Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a
- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (562–576)  
**Author Location** gp41 (562–576 IIIB, B10)  
**Epitope** QQHLLQLTVWGIKQL  
**Immunogen** HIV-1 infection

- Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a
- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (562–576)  
**Author Location**  
**Epitope** QQHLLQLTVWGIKQL  
**Immunogen**

**Species (MHC)**

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 25/50 Brazilian sequences; variant QQHm-LQLTVWGIKQL has high frequency in subtypes B, C, and BF recombinant sequences.

**HXB2 Location** gp160 (570–589)

**Author Location** gp41 (MN)  
**Epitope** VWGIKQLQARVLAVERYLKD  
**Epitope name** VD20

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR)

**Assay type** Cytokine production, proliferation, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**References** Malhotra *et al.* 2003

- 92 acute- or early-HIV infected subjects were tested for Env- and Gag-specific Th responses. There was an overall low probability of detecting HIV-1-specific Th responses, Env responses were rare and (5%) and only detected very early in infection, probably reflecting a low frequency of response and impaired lymphoproliferative capacity, not viral escape. Gag-specific Th responses were observed more frequently (16%), were found throughout the acute and early infection phases, and predominated after ARV therapy.
- This epitope is one of six Env-specific Th responses detected in one patient 11 days post-infection that were studied in detail. The CD4+ clones showed MHC-restricted cytotoxicity and secreted high levels of cytokines when stimulated. These Th responses were not detected at subsequent time points, despite the Env specific Th cells being maintained as detected by TCR clonal transcripts, and the epitope sequence being maintained in Env.
- This peptide showed promiscuous binding to DRB1\*0101, DRB1\*1101, DRB1\*1302, DRB1\*0701, DRB1\*0801 DRB4\*0101 DRB5\*01.

**HXB2 Location** gp160 (572–591)

**Author Location** gp41 (572–591)  
**Epitope** GIKQLQARILAVERYLKDQQ  
**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)

**References** Brown *et al.* 1995

- This peptide was a good immunogen in BALB/c and CBA mice, producing a strong proliferative response.
- At least one of the four residues GIKQ enhances stimulation, and in CBA mice these residues influence the ability to prime T-cells *in vivo*.
- QLQARILAVERY stimulated the greatest *in vitro* T-cell response.
- VERYLKDQQ was the minimal reactive sequence recognized by a T-cell line.

**HXB2 Location** gp160 (576–591)

**Author Location** gp41 (576–591)

**Epitope** LQARILAVERYLKDQQ

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)

**References** Brown *et al.* 1995

- This peptide was a poor immunogen in BALB/c and CBA mice used in this experiment, producing a weak proliferative response.

**HXB2 Location** gp160 (578–608)

**Author Location** gp41 (585–615 IIIB)

**Epitope** ARILAVERYLKDQQLLGIWGCSGKLICTTAV

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse

**References** Goodman-Snitkoff *et al.* 1990

- Identification of putative Th epitopes that can stimulate an antibody response in peptide immunized mice.

**HXB2 Location** gp160 (579–601)

**Author Location** gp41 (579–601)

**Epitope** RILAVERYLKDQQLLGGIWGCSGK

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)

**References** Brown *et al.* 1995

- This peptide was a good immunogen in BALB/c and CBA.
- This peptide produced a strong Th response in both mice strains which was more responsive towards GIKQLQARILAVERYLKDQQ and LQARILAVERYLKDQQ than to immunizing peptide.

**HXB2 Location** gp160 (579–604)

**Author Location** gp41 (584–609 LAI)

**Epitope** RILAVERYLKDQQLLGIWGCSGKLIC

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** gp160 (586–597)

**Author Location** Env (586–598)

**Epitope** YLRDQQLLGIWG

**Immunogen** HIV-1 infection

**Species (MHC)** human, chimpanzee

**References** Nehete *et al.* 1998b

- HIV-infected chimpanzees and HIV-positive patients show positive proliferative responses to multiple peptides from five conserved regions of the HIV-1 Env.

**HXB2 Location** gp160 (586–598)

**Author Location** Env (586–598)

**Epitope** YLRDQQLLGIWGC

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (MHC)** macaque, mouse

**References** Nehete *et al.* 1993

- Synthetic peptide derived from conserved region of the HIV-1 envelope that stimulates a proliferative response in mice.
- Proliferative response to this peptide was observed in 1/3 immunized rhesus monkeys, with a weak transient response in the other two.

**HXB2 Location** gp160 (593–604)

**Author Location** gp41 (598–609 LAV-1)

**Epitope** LGLWGCSGKLIC

**Immunogen** vaccine

**Species (MHC)** mouse (H2<sup>d</sup>)

**References** Schrier *et al.* 1988

- Murine T-dependent B-cell response – 7/29 had a proliferative response to this peptide.

**HXB2 Location** gp160 (593–604)

**Author Location** gp41 (593–604 IIIB)

**Epitope** LGIWGCSGKLIC

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Bell *et al.* 1992

- Elicits T-cell proliferation and B cell responses, but only during the asymptomatic phase of HIV infection.

**HXB2 Location** gp160 (593–604)

**Author Location**

**Epitope** LGIWGCSGKLIC

**Immunogen**

**Species (MHC)**

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 27/50 Brazilian sequences.

**HXB2 Location** gp160 (594–603)

**Author Location** gp41 (594–603 IIIB)

**Epitope** GIWGCSGKLI

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Kelleher *et al.* 1998b

- Epitope documented as a “previously described” epitope Bell *et al.* [1992], but in Bell *et al.* it was described as gp41(594–603 IIIB), LGIWGCSGKLIC.
- Immunization with a p24-VLP virus-like particle did not significantly impact CD4+ lymphocyte count, viral load, or p24 antibody titre.
- Immunization with p24-VLP did not increase the proliferative response to this gp41 epitope, however, there was a modest, short-lived increased proliferative response to p24.

**HXB2 Location** gp160 (594–603)

**Author Location**

**Epitope** GIWGCSGKLI

**Immunogen**

**Species (MHC)**

**Keywords** subtype comparisons, viral fitness and reversion

**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 27/50 Brazilian sequences.

**HXB2 Location** gp160 (594–604)**Author Location** gp41 (consensus)**Epitope** GIWGCSGKLIC**Immunogen** HIV-1 infection**Species (MHC)** human**References** Mutch *et al.* 1994

- Core region of peptides that can stimulate proliferative responses from seronegative and seropositive people.

**HXB2 Location** gp160 (594–604)**Author Location****Epitope** GIWGCSGKLIC**Immunogen****Species (MHC)****Keywords** subtype comparisons, viral fitness and reversion**References** de Queiroz *et al.* 2007

- Determined the frequencies of known CD8+ and CD4+ Env epitope sequences among Brazilian HIV sequences of various subtypes.
- Present in 27/50 Brazilian sequences.

**HXB2 Location** gp160 (598–609)**Author Location** gp41 (603–614 LAI)**Epitope** CSGKLICTTAVP**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** gp160 (604–615)**Author Location** gp41 (609–620 LAI)**Epitope** CTTAVPWNASWS**Subtype** B**Immunogen** HIV-1 infection**Species (MHC)** human**References** Schrier *et al.* 1989

- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** gp160 (606–620)**Author Location** gp41 (1035)**Epitope** TNVPWNASWSNKSLE**Subtype** B**Immunogen** vaccine*Vector/Type:* vaccinia prime with gp120 boost *Strain:* B clade 1035 *HIV component:* Env *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (Class II I Ab)**Assay type** T-cell Elispot**Keywords** epitope processing, vaccine-induced epitopes, escape, TCR usage**References** Zhan *et al.* 2003

- A very narrow Th response was stimulated in C57BL/6 mice vaccinated with vaccinia expressed HIV-1 env clone 1035, to the peptide PKVSFEPPIHYCAP, located in the C2 region of gp120. The only other peptide recognized using Elispot on Env overlapping peptides to test vaccine responses in the mice was this one: TNVPWNASWSNKSLE, located in gp41.

**HXB2 Location** gp160 (606–620)**Author Location** gp41 (UG92005)**Epitope** TNVPWNASWSNKSLE**Immunogen** vaccine*Vector/Type:* DNA, protein, vaccinia*Strain:* B clade 1007, D clade UG92005*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)**Species (MHC)** mouse (H-2 IA<sup>b</sup>)**Keywords** subtype comparisons, epitope processing, TCR usage**References** Surman *et al.* 2001

- This gp140 epitope of UG92005 (UG, clade D) was recognized by five hybridomas with V $\beta$  usage V $\beta$  8.1, 14 and not determined – one of the V $\beta$  8.1 was shown to utilize V $\alpha$  8.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given i.m., 3-4 weeks later boosted with VV, and 3-4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (609–616)**Author Location** gp41 (consensus)**Epitope** PWNASWSN**Immunogen** HIV-1 infection**Species (MHC)** human**References** Mutch *et al.* 1994

- Core region of peptides that can stimulate proliferative responses from seronegative and seropositive people.

**HXB2 Location** gp160 (611–620)  
**Author Location** gp41 (1007, UG92005)  
**Epitope** NASWSNKSLE

**Immunogen** vaccine  
*Vector/Type:* DNA, protein, vaccinia  
*Strain:* B clade 1007, D clade UG92005  
*HIV component:* gp140 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2 IA<sup>b</sup>)  
**Keywords** subtype comparisons, epitope processing, TCR usage

**References** Surman *et al.* 2001

- This gp41 epitope is conserved in 1007 (US, clade B) and UG92005 (UG, clade D) and was recognized by two hybridomas from two different mice that were vaccinated with different clades – the V $\beta$  usage was V $\beta$  4 and 14.
- The epitope described here is the region of overlap of two 15 mers that were both able to stimulate IL-2 production from the hybridoma (T[*TN*]VPWNASWSNKSLE and NASWSNKSLEQIWN) – the only difference between 1007 and UG92005 for these two proteins is that 1007 has a T and UG92005 has an N in the second position of the first peptide.
- C57BL/6 mice were immunized with a prime-boost strategy involving three HIV-1 Env antigens: Mice were primed with DNA given *i.m.*, 3–4 weeks later boosted with VV, and 3–4 weeks later boosted again with purified protein in Freund's adjuvant.
- The vaccinia construct is a pSC11-based VV vector with the first 38 amino acids contributed by BH10 and the rest of gp120 and gp41 by the vaccine strain, the DNA construct is in the pJW4303 vector with a CMV promoter, and the purified protein is expressed from the pJW4303 vector transfected into CHO-K1 cells.
- Ten days after the final boost, hybridomas were made and tested for IL-2 production using either B6 spleen cells or H-2 IA<sup>b</sup> transfected L cells as targets and V $\beta$  usage was determined.
- Mice were immunized with an Env from either one of two clades: HIV-1 1007, a clade B strain isolated from an individual from Memphis Tennessee, and HIV-1 92UG005, a clade D vaccine isolated from Uganda in 1992 through the WHO.
- 80 unique clonotypes were characterized from six mice.
- H-2 IA<sup>b</sup> restricted T-helper epitopes were concentrated in 5 distinct regions within the Env sequence (2 clonotype responses in V2, 26 in C2, 22 in V3, 23 in V4C4, and 7 in gp41).
- Epitope hotspots tended to be proximal to heavily glycosylated regions of the Env sequence, in exposed, non-helical strands of the protein. The non-uniform localization may be influenced by differential antigen processing and the glycosylation site proximity may allow binding to lectins and promote trafficking through processing pathways.

**HXB2 Location** gp160 (614–629)  
**Author Location** gp41 (IIIB)  
**Epitope** WSNKSLEDIWDMTWC

**Immunogen** *in vitro* stimulation or selection  
**Species (MHC)** human

**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.

- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (620–634)  
**Author Location** Env (620–634 HXB2)  
**Epitope** EQIWNHTTWMEWDRE  
**Subtype** B

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (DP4)  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, epitope processing, computational epitope prediction, dendritic cells

**References** Cohen *et al.* 2006

- Motif-based quantitative matrices binding predictions, binding assays and cellular assays were used to identify 4 HLA-DP4 epitopes by scanning the whole HIV-1 genome.
- 21 peptides were predicted to bind HLA-DP4, 17 of them did bind in binding assays, 6 of them were good binders. Of the 6 good binders, 4 peptides primed peptide-specific CD4+ T cell lines restricted to HLA-DP4 molecules.

**HXB2 Location** gp160 (634–649)  
**Author Location** gp41 (IIIB)  
**Epitope** EIDNYTNTIYTLLEEC

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human  
**References** Manca *et al.* 1995b  
 • Peptide stimulation of PBMC from non-infected individuals *in vitro*.  
 • Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (647–661)  
**Author Location** gp41 (647–661 IIIB, B10)  
**Epitope** EESQNQEKNEQELL

**Immunogen** HIV-1 infection

**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a  
 • 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (650–662)  
**Author Location** gp41 (655–667 LAI)  
**Epitope** QNQQEKNEQELLE  
**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human  
**References** Schrier *et al.* 1989  
 • Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** gp160 (667–681)  
**Author Location** gp41 (667–681 IIIB, B10)  
**Epitope** ASLWNWFNITNWLWY

**Immunogen** HIV-1 infection

**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a  
 • 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (682–696)  
**Author Location** gp41 (682–696 IIIB, B10)

- Epitope** IKLFIMIVGGLVGLR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a
- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

**HXB2 Location** gp160 (688–710)

**Author Location**

- Epitope** IVGGLIGLRIVFAVLSIVNRVRQ  
**Epitope name** HIV-VAX-1058  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB\*0101)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design  
**References** De Groot *et al.* 2005
- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
  - 1/13 US test subjects responded to this 23-mer by CD4 Elispot assay. The core computer-predicted peptide was LRIVFAVLS.

**HXB2 Location** gp160 (696–718)

**Author Location**

- Epitope** RIVFAVLSIVNRVRQGYSPLSFQ  
**Epitope name** HIV-VAX-1061  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB\*0101)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design  
**References** De Groot *et al.* 2005
- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
  - 2/13 US test subjects responded to this 23-mer by CD4 Elispot assay. The core computer-predicted peptide was SIVNRVRQG.

**HXB2 Location** gp160 (724–745)

**Author Location** gp41 (731–752)

- Epitope** PRGPDPRPEGIEEEGGERDRDRS  
**Immunogen** vaccine  
*Vector/Type:* peptide in cowpea mosaic virus (CPMV) *HIV component:* gp41 *Adjuvant:* Quillaja saponin (Quil-A)  
**Species (MHC)** mouse (H-2<sup>k</sup>)  
**Keywords** Th1  
**References** McInerney *et al.* 1999
- A gp41 peptide was expressed in a cowpea mosaic virus (CPMV) and mice were vaccinated with a purified chimeric particle – out of five adjuvants tested, only Quil A could stimulate anti-gp41 antibodies and an *in vitro* proliferative response.

- The antibodies were predominantly IgG2a, suggesting a Th1 response.

**HXB2 Location** gp160 (732–744)

**Author Location** gp41 (737–749 LAI)

- Epitope** GIEEEGGERDRDR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Schrier *et al.* 1989
- Stimulates T-cell proliferation in HIV-infected donors.

**HXB2 Location** gp160 (761–783)

**Author Location**

- Epitope** RSLCLFSYHRLRDLILLIVTRIVE  
**Epitope name** HIV-VAX-1059  
**Immunogen** HIV-1 infection  
**Species (MHC)** human (DRB\*0101)  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design  
**References** De Groot *et al.* 2005
- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
  - 4/13 US test subjects responded to this 23-mer by CD4 Elispot assay. The core computer-predicted peptide was YHRLRDLILL.

**HXB2 Location** gp160 (772–787)

**Author Location** gp41 (261–276 clade B consensus)

- Epitope** RDLLLVTRIVELLGR  
**Subtype** B  
**Immunogen** HIV-1 infection, computer prediction  
**Species (MHC)** human (DRB1\*0101, DRB1\*0701, DRB1\*1101)  
**Country** Brazil  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding  
**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA  
**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While RDLLLVTRIVELLGR was the reacting peptide, shorter LLLVTRIVELL peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of *in vitro* peptide presentation to CD4 T cells.

**HXB2 Location** gp160 (780–794)

**Author Location** gp41 (787–801 IIIB)

- Epitope** RIVELLGRRGWEALK  
**Immunogen** vaccine



- Strain:* B clade IIIB *HIV component:* gp160
- Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>t4</sup>)
- References** Hale *et al.* 1989
- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.
- HXB2 Location** gp160 (780–794)
- Author Location** gp160 (787–801 IIIB)
- Epitope** RIVELLGRRGWEALK
- Immunogen** vaccine
- Vector/Type:* protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
- Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)
- References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a
- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.D2 mice (H-2A<sup>d</sup>, E<sup>d</sup>), and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)
  - RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes including RIVELLGRRGWEALK and is referred to as a "multideterminant region" or cluster peptide, but the longer peptide only stimulates cells from H-2<sup>k</sup> mice.
- HXB2 Location** gp160 (780–813)
- Author Location** gp160 (787–820 IIIB)
- Epitope** RIVELLGRRGWEALKYWWNLLQYWSQELKNSA-VS
- Immunogen** HIV-1 infection, vaccine
- Vector/Type:* protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
- Species (MHC)** mouse (H-2<sup>k</sup>)
- References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a
- RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
  - Six multideterminant region cluster peptides were evaluated Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
  - This cluster peptide elicited proliferative responses in cells from only B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), and not from B10.D2 mice (H-2A<sup>d</sup>, E<sup>d</sup>), B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>), or B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)
  - IL-2 production in response to this peptide was observed in 59% (17/29) of asymptomatic HIV-infected individuals.
- HXB2 Location** gp160 (794–808)
- Author Location** gp41 (801–815 IIIB)
- Epitope** KYWWNLLQYWSQELK
- Immunogen** vaccine
- Strain:* B clade IIIB *HIV component:* gp160
- Species (MHC)** mouse (H-2<sup>k</sup>)
- References** Hale *et al.* 1989
- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

- HXB2 Location** gp160 (794–808)
- Author Location** gp160 (801–815 IIIB)
- Epitope** KYWWNLLQYWSQELK
- Immunogen** vaccine
- Vector/Type:* protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
- Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)
- References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a
- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.D2 mice (H-2A<sup>d</sup>, E<sup>d</sup>), and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)
  - RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes including KYWWNLLQYWSQELK and is referred to as a "multideterminant region" or cluster peptide, but the longer peptide only stimulates cells from H-2<sup>k</sup> mice.
- HXB2 Location** gp160 (799–813)
- Author Location** gp160 (806–820 IIIB)
- Epitope** LLQYWSQELKNSAVS
- Immunogen** vaccine
- Vector/Type:* protein *Strain:* B clade IIIB *HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)
- Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)
- References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a
- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.D2 mice (H-2A<sup>d</sup>, E<sup>d</sup>), and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)
  - RIVELLGRRGWEALKYWWNLLQYWSQELKNSAVS encompasses several murine Th epitopes including LLQYWSQELKNSAVS and is referred to as a "multideterminant region" or cluster peptide, but the longer peptide only stimulates cells from H-2<sup>k</sup> mice.
- HXB2 Location** gp160 (799–813)
- Author Location** gp41 (806–820 IIIB)
- Epitope** LLQYWSQELKNSAVS
- Immunogen** vaccine
- Strain:* B clade IIIB *HIV component:* gp160
- Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>t4</sup>)
- References** Hale *et al.* 1989
- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.
- HXB2 Location** gp160 (799–813)
- Author Location** gp41 (806–820 IIIB)
- Epitope** LLQYWSQELKNSAVS
- Immunogen** vaccine
- Strain:* B clade IIIB *HIV component:* gp160
- Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>t4</sup>)
- References** Hale *et al.* 1989
- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (814–829)  
**Author Location** gp41 (IIIB)  
**Epitope** WLNATAIAVTEGTRDC  
**Immunogen** *in vitro* stimulation or selection  
**Species (MHC)** human  
**References** Manca *et al.* 1995b

- Peptide stimulation of PBMC from non-infected individuals *in vitro*.
- Peptide priming does not always induce T-cells that recognize whole protein.

**HXB2 Location** gp160 (821–835)  
**Author Location** gp41 (828–842 IIIB)  
**Epitope** AVAEGTDRVIEVVQG  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>k</sup>)  
**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (821–835)  
**Author Location** gp160 (828–842 IIIB)  
**Epitope** AVAEGTDRVIEVVQG  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)  
**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>), and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)
- AVAEGTDRVIEVVQGAYRAIRHIPP RRIRQGLER encompasses several murine Th epitopes including AVAEGTDRVIEVVQG and is referred to as a "multideterminant region" or cluster peptide.

**HXB2 Location** gp160 (821–838)  
**Author Location** gp41 (827–843)  
**Epitope** YVAEGTDRVIEVVQACR  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Keywords** rate of progression  
**References** Caruso *et al.* 1997

- As HIV-1-infected individuals progress to disease, T-cells show reduced ability to proliferate in response to HIV antigen, but retain the ability to express the activation antigens CD25 and CD71.
- The ability to express activation markers in response to HIV is retained, but the response to tetanus toxoid recall antigen is lost.
- This study investigated CD25 and CD71 expression in PBMC from patients at various stages of progression, measuring the response to *in vitro* stimulation by peptide cocktail containing four antigenic Env peptides, or p17 and p24.

**HXB2 Location** gp160 (821–853)

**Author Location** gp160 (828–860 IIIB)  
**Epitope** AVAEGTDRVIEVVQGAYRAIRHIPP RRIRQGLER  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** human, mouse (H-2<sup>b</sup>, H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)  
**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- AVAEGTDRVIEVVQGAYRAIRHIPP RRIRQGLER encompasses several murine Th epitopes and is referred to as a "multideterminant region" or cluster peptide.
- Six multideterminant region cluster peptides were evaluated for Th responses in different MHC/HLA backgrounds after vaccination of mice with gp160, or in infected people.
- This cluster peptide elicited proliferative responses in cells from all four MHC types tested: B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.D2 mice (H-2A<sup>d</sup>, E<sup>d</sup>), B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>), and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)
- IL-2 production in response to this peptide was observed in only 8% (1/12) of asymptomatic HIV-infected individuals.

**HXB2 Location** gp160 (827–835)  
**Author Location** gp41 (834–842 IIIB)  
**Epitope** DRVIEVVQG  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>k</sup>)  
**References** Hale *et al.* 1989

- Suggested H-2<sup>k</sup> epitope based on region of overlap.

**HXB2 Location** gp160 (827–841)  
**Author Location** gp160 (834–848 IIIB)  
**Epitope** DRVIEVVQGAYRAIR  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>k</sup>)  
**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>) and B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>)

**HXB2 Location** gp160 (827–841)  
**Author Location** gp41 (834–848 IIIB)  
**Epitope** DRVIEVVQGAYRAIR  
**Epitope name** TH4  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* gp160  
**Species (MHC)** mouse (H-2<sup>i5</sup>, H-2<sup>k</sup>)  
**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.
- Called Th4.1 and TH4.

**HXB2 Location** gp160 (827–841)  
**Author Location** gp41 (834–848 IIIB)

- Epitope** DRVIEVVQGAYRAIR  
**Epitope name** TH4  
**Immunogen** vaccine  
*Vector/Type:* peptide prime with protein boost *Strain:* B clade IIIB *HIV component:* gp160  
**Species (MHC)** macaque  
**References** Hosmalin *et al.* 1991
- Peptide priming to induce T-cell help enhances antibody response to gp160 immunization.
  - Called Th4.1 and TH4.
- HXB2 Location** gp160 (827–841)  
**Author Location** gp41 (834–848 IIIB)  
**Epitope** DRVIEVVQGAYRAIR  
**Epitope name** TH4  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Clerici *et al.* 1997
- used in a study of the influence of pentoxifylline on HIV specific T-cells.
- HXB2 Location** gp160 (827–841)  
**Author Location** gp41 (834–848 IIIB)  
**Epitope** DRVIEVVQGAYRAIR  
**Epitope name** TH4  
**Immunogen** human  
**Species (MHC)** human  
**References** Pinto *et al.* 1995
- CTL activity analyzed in parallel with Th reactivity in exposed but uninfected health care workers.
  - Called Th4.1 and TH4.
- HXB2 Location** gp160 (827–841)  
**Author Location** gp41 (834–848 IIIB)  
**Epitope** DRVIEVVQGAYRAIR  
**Epitope name** TH4  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Clerici *et al.* 1991a
- Peptides stimulate Th cell function and CTL activity in similar patient populations.
  - Called Th4.1 and TH4.
- HXB2 Location** gp160 (827–841)  
**Author Location** gp41 (834–848 IIIB)  
**Epitope** DRVIEVVQGAYRAIR  
**Epitope name** TH4  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB *HIV component:* gp160  
**Species (MHC)** human  
**References** Clerici *et al.* 1991b
- Immunizing uninfected individuals with rgp160 results in stronger Th response than does natural infection.
  - Called Th4.1 and TH4.
- HXB2 Location** gp160 (827–841)  
**Author Location** gp41 (834–848 IIIB)  
**Epitope** DRVIEVVQGAYRAIR

- Epitope name** TH4  
**Immunogen**  
**Species (MHC)** human  
**References** Clerici *et al.* 1992
- Cell-mediated immune response to HIV-1 peptides in HIV-1 exposed seronegative men.
  - Called Th4.1 and TH4.
- HXB2 Location** gp160 (827–841)  
**Author Location** gp41 (834–848 IIIB)  
**Epitope** DRVIEVVQGAYRAIR  
**Epitope name** TH4  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Clerici *et al.* 1989
- IL-2 production detection of Th lymphocytes from asymptomatic HIV-positive individuals.
  - Called Th4.1 and TH4.
- HXB2 Location** gp160 (827–841)  
**Author Location** gp41 (834–848 IIIB)  
**Epitope** DRVIEVVQGAYRAIR  
**Epitope name** TH4  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**References** Kaul *et al.* 1999
- Kenyan sex workers that remained seronegative were found to frequently have HIV-env peptide specific Th responses detected by an IL-2 assay (11/20 cases) and mucosal genital tract anti-HIV IgA (16/21 cases)
  - Helper epitopes used in this study were noted to be previously described Clerici *et al.* [1989], and were not explicitly described in Kaul *et al.* [1999]
- HXB2 Location** gp160 (827–841)  
**Author Location** gp41  
**Epitope** DRVIEVVQGAYRAIR  
**Epitope name** TH4, Th4.1  
**Immunogen** HIV-1 infection, HIV-1 exposed seronegative  
**Species (MHC)** human  
**Keywords** subtype comparisons, responses in children, mother-to-infant transmission  
**References** Kuhn *et al.* 2001a
- In a S. African perinatal transmission study, 33% (33/86) of cord blood samples from infants with seropositive mothers produced T-helper responses (measured by a bioassay measuring IL2 production in a murine cell line and confirmed with a proliferation assay) against a peptide cocktail containing Th epitopes P18 MN, P18 IIIB, T1, T2, and TH4.
  - The mothers were predominantly infected with subtype C, but the T help response was detectable in a number of cord blood samples despite using peptides based on B subtype reagents.
  - 3/33 infants with cord blood T help responses to Env were infected *in utero*, 2/33 were lost to follow up, and 28/33 were not infected. 6/53 of the infants with cord blood that was unresponsive to Env peptide stimulation were infected before delivery, and 8/47 contracted HIV intrapartum or via breast-feeding.

- Measurable HIV specific T help responses elicited in the immunologically immature newborn, possibly in response to *in utero* exposure, are associated with a protective natural immunity that helps block mother-infant transmission of HIV-1.

**HXB2 Location** gp160 (827–841)

**Author Location** Env (834–848 IIIB)

**Epitope** DRVIEVVQGAYRAIR

**Epitope name** TH4.1

**Immunogen** HIV-1 infection, HIV-1 exposed seronegative

**Species (MHC)**

**Assay type** Cytokine production

**Keywords** mother-to-infant transmission

**References** Clerici *et al.* 1993a

- Cord blood samples in 8/23 infants with HIV+ mothers showed IL-2 production in response to peptides from HIV-1 gp1260, demonstrating that Th cell priming to HIV env determinants can occur in utero. HIV-specific Th immunity in utero may be protective, as none of the 8 with HIV-1 specific Th activity became infected, while 3/15 infants with no detectable Th activated were infected.
- PBL from 10/21 of the mother showed HIV-1 specific Th activity through IL-2 production in response to Env peptides.

**HXB2 Location** gp160 (827–841)

**Author Location** Env (IIIB)

**Epitope** DRVIEVVQGAYRAIR

**Epitope name** TH4.1

**Subtype** B

**Immunogen** HIV-1 exposed seronegative

**Species (MHC)**

**Assay type** Cytokine production

**References** Clerici *et al.* 1994a

- Six of eight HIV-exposed health care workers had transient HIV-specific T-helper responses after percutaneous exposure to HIV, responding to two or more Env peptides among the set T1, T2, TH4.1, P18IIIB and P18MN. Responses were lost after 12–56 weeks. The HIV-specific Th responses occurred without seroconversion or PCR evidence for infection.
- Six of the eight HIV-exposed individuals responded to two or more peptides, whereas, only one individual exposed to HIV-negative blood responded to one peptide.

**HXB2 Location** gp160 (827–841)

**Author Location** HIV-1 (IIIB)

**Epitope** DRVIEVVQGAYRAIR

**Epitope name** TH4.1

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)**

**Assay type** Cytokine production

**References** Clerici *et al.* 1994b

- IL-10-specific mRNA was upregulated in PBMC from asymptomatic, HIV-infected (HIV+) patients, and was particularly high in those with severely compromised Th cells function. Th response to HIV peptides *in vitro* could be restored by IL-10 Ab.

**HXB2 Location** gp160 (827–841)

**Author Location** Env (834–848)

**Epitope** DRVIEVVQGAYRAIR

**Epitope name** TH4-1

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** proliferation

**Keywords** responses in children, mother-to-infant transmission

**References** Kuhn *et al.* 2001b

- Th proliferative responses in cord blood at delivery to a cocktail of HIV envelope peptides were infrequent (1/41) among infants whose HIV-positive mothers received antiretroviral prophylaxis at delivery to prevent transmission. Responses were 10 times more frequent among infants of HIV-seropositive women who had no antiretroviral treatment (7/29). Reductions of HIV-specific responses occurred despite persistence of detectable HIV RNA in the mothers at delivery.
- The reduction of Th responses in newborns raises the possibility that anti-retroviral exposure during pregnancy may block subsequent immune protection. The authors point two relevant citations that showed ARV exposed infants had a more rapid course of progression (Kuhn *et al.*, JID 182:104 (2000)), but were at no greater risk of infection due to subsequent breast feeding (Ditrane *et al.*, Lancet 354:2050 (1999)).

**HXB2 Location** gp160 (827–841)

**Author Location** Env (gp160) (421–436)

**Epitope** DRVIEVVQGAYRAIR

**Epitope name** TH4.1

**Subtype** C

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** South Africa

**Assay type** proliferation

**Keywords** responses in children, variant cross-recognition or cross-neutralization

**References** Meddows-Taylor *et al.* 2004

- Viral isolates (gp160) from 16 vertically HIV-1 infected children (8 T-helper cell Env responders and 8 non-responders) were analyzed for variation after comparison with Env peptide sequences (conserved regions T1, T2 and TH4.1, hyper-variable regions P18 MN and P181 IIIB) used for *in vitro* stimulation.
- No correlation between the age, clinical category (mild or severe), HIV-1 viral load and the degree of epitope variation was established.

**HXB2 Location** gp160 (827–853)

**Author Location** Env (HIV-1 IIIB)

**Epitope** DRVIEVVQGAYRAIRHIPRRIRQGLER

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB, SIV *HIV component:* Env, Gag, Pol *Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72), Montanide (ISA 51)

**Species (MHC)** macaque

**Assay type** proliferation

**Keywords** mucosal immunity

**References** Belyakov *et al.* 2001

- Different HIV strains were used for different regions: env HIV-1 IIIB, gag SIV, pol SIV
- Intrarectal vaccination with a Th and CTL peptide vaccine provided better protection against intrarectal challenge with pathogenic SHIV-Ku1 than subcutaneous administered vaccine. In some animals after the initial viremia, viral loads were diminished to undetectable levels in the blood and intestine, and CD4+ T cells were better preserved.
- The CD4 T-cell proliferative response correlated with the level of the CTL response.

**HXB2 Location** gp160 (829–843)

**Author Location** gp160 (836–850 IIIB)

**Epitope** VIEVVQGYAIRAIRHI

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>k</sup>)

**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>) and B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>)

**HXB2 Location** gp160 (834–841)

**Author Location** gp41 (841–848 IIIB)

**Epitope** QGAYRAIR

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>i5</sup>)

**References** Hale *et al.* 1989

- Suggested H-2<sup>k</sup> epitope based on region of overlap.

**HXB2 Location** gp160 (834–848)

**Author Location** gp41 (841–855 IIIB)

**Epitope** QGAYRAIRHIPRRIR

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>i5</sup>, H-2<sup>t4</sup>)

**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (834–848)

**Author Location** gp160 (841–855 IIIB)

**Epitope** QGAYRAIRHIPRRIR

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)

**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>), B10.D2(H-2A<sup>d</sup>, E<sup>d</sup>), and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)

**HXB2 Location** gp160 (834–853)

**Author Location** Env

**Epitope** QGAYRAIRHIPRRIRQGLER

**Immunogen** vaccine

*Vector/Type:* ISCOM *Strain:* multiple epitope immunogen *HIV component:* Env, Gag, Tat

**Species (MHC)** macaque

**Assay type** Other

**Keywords** vaccine antigen design

**References** Pahar *et al.* 2006

- Rhesus macaques were immunized intrarectally with an ISCOM vaccine containing a single SIV-Gag CTL epitope, a single human HIV-Env Th epitope, plus a negative control mouse H-2d Tat epitope. Following challenge with SHIV-SF162p4, immunized macaques became infected, but had significantly lower viral loads than non-immunized animals.

**HXB2 Location** gp160 (839–848)

**Author Location** gp41 (846–855 IIIB)

**Epitope** AIRHIPRRIR

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>t4</sup>)

**References** Hale *et al.* 1989

- Suggested H-2<sup>d,t4</sup> epitope based on region of overlap.

**HXB2 Location** gp160 (839–853)

**Author Location** gp41 (846–860 IIIB)

**Epitope** AIRHIPRRIRQGLER

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* gp160

**Species (MHC)** mouse (H-2<sup>d</sup>, H-2<sup>t4</sup>)

**References** Hale *et al.* 1989

- Six multideterminant helper T-cell regions are recognized by mice of three or four MHC types.

**HXB2 Location** gp160 (839–853)

**Author Location** gp160 (828–842 IIIB)

**Epitope** AIRHIPRRIRQGLER

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** human, mouse (H-2<sup>b</sup>, H-2<sup>k</sup>, H-2<sup>s</sup>)

**References** Berzofsky *et al.* 1991b; Berzofsky *et al.* 1991a

- This peptide elicited proliferative responses in cells from B10.BR mice (H-2A<sup>k</sup>, E<sup>k</sup>), B10.A(5R) mice (H-2A<sup>b</sup>, E<sup>b</sup>), and B10.S(9R) mice (H-2A<sup>s</sup>, E<sup>s</sup>)

**HXB2 Location** gp160 (842–856)

**Author Location** gp41 (842–856 IIIB, B10)

**Epitope** HIPRRIRQGLERILL

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Wahren *et al.* 1989b; Wahren *et al.* 1989a

- 12 gag and 18 env peptides were identified that could commonly evoke T-cell responses.

## III-B-17 Env Helper/CD4+ T-cell epitopes

**HXB2 Location** Env**Author Location** gp120**Epitope****Immunogen** vaccine*Vector/Type:* DNA *HIV component:* Env, Gag, Pol *Adjuvant:* IFN $\gamma$ , IL-2, IL-4**Species (MHC)** mouse (H-2<sup>d</sup>)**Keywords** Th1**References** Kim *et al.* 2000

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of Th1 cytokine IFN- $\gamma$  drove Th1 immune responses and enhanced CTL responses.

**HXB2 Location** Env**Author Location** gp120 (IIIB)**Epitope****Immunogen** vaccine*Vector/Type:* vaccinia *Strain:* B clade IIIB *HIV component:* gp160**Species (MHC)** mouse (H-2<sup>d</sup>)**Keywords** Th1, Th2**References** Shirai *et al.* 2001

- Helicobacter pylori induces Th1 responses early, but predominantly Th2 responses later in infection (at 6 weeks) – differentiation of HIV-1 gp160 CD4+ help and CD8+ CTL effector cells in response to HIV gp160-vaccinia vaccination is impaired in BALB/c mice infected with H. pylori.

**HXB2 Location** Env**Author Location** gp120 (V3) and p24 (IIIB, MN, BH10)**Epitope****Subtype** A, B**Immunogen** vaccine*Vector/Type:* virus-like particle (VLP) *Strain:* A clade UG5.94UG018, B clade IIIB *HIV component:* Gag, gp120**Species (MHC)** mouse (H-2<sup>d</sup>)**Keywords** subtype comparisons**References** Buonaguro *et al.* 2002

- Different HIV strains were used for different regions: gp120 A clade UG5.94UG018; Gag HIV-1 IIIB
- BALB/c mice were given intraperitoneal immunization in the absence of adjuvants with virus-like particles (VLPs) expressing recombinant subtype A gp120 and Pr55gag.
- High dose-independent humoral responses were elicited against both gp120 and p24 peptides, and CTL responses were observed against target cells carrying vaccinia expressed gp120 and Gag.
- Recombinant rgp120 (clade B, MN) induced T cell proliferative responses *in vitro* from vaccinated animals.

**HXB2 Location** Env**Author Location** gp160 (IIIB)**Epitope****Immunogen** vaccine*Vector/Type:* peptide, protein *Strain:* Bclade IIIB *HIV component:* gp160, V3*Adjuvant:* E. coli mutant heat labile enterotoxin (LT-R72)**Species (MHC)** mouse (H2<sup>d</sup>)**Keywords** Th1, Th2**References** Morris *et al.* 2000

- Mice were intranasally immunized with 20 ug of HIV-gp160 and 5 ug of peptide E7 (RIHIGPGRAFYAARK) with the adjuvant LT(R192G), a heat-labile enterotoxin produced by E. coli.
- Adjuvant LT(R192G) was required for stimulation of antigen-specific IgG1, IgG2 antibodies, and Th1 and Th2 cytokine responses to gp160, and peptide-specific CTL responses.
- Increased IFN- $\gamma$ , IL-10 and IL-6 cytokine production specific to gp160 was measured with co-immunization of gp160 with LT(R192G)

**HXB2 Location** Env**Author Location** gp160 (IIIB)**Epitope****Immunogen** vaccine*Vector/Type:* DNA with CMV promotor *Strain:* B clade IIIB *HIV component:* gp160, Rev *Adjuvant:* Br-cAMP**Species (MHC)** mouse (H2<sup>d</sup>)**Keywords** Th1**References** Arai *et al.* 2000

- The CMV promotor responds to the intracellular level of cAMP, and 8 Br-cAMP can increase transgene expression so it was co-administered with a CMV-based DNA vaccine both intranasally and intramuscularly.
- 8 Br-cAMP increased serum IgG responses, HIV-specific CTL, DTH and Th1 responses, and IgA in the intranasal vaccination.
- A CAT assay study showed adjuvant effect was due to CMV promotor activation.

**HXB2 Location** Env**Author Location** gp120 (IIIB)**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade IIIB *HIV component:* gp120, gp160**Species (MHC)** mouse**Keywords** Th1**References** Shiver *et al.* 1997

- DNA vaccinations of BALBc mice with a gp120 or gp160 DNA vaccine elicited a strong T-cell proliferative response with Th1-like secretion of  $\gamma$  interferon and IL-2, with little or no IL-4, as well as antigen specific gp120 Abs.
- An intramuscular route of inoculation gave a stronger proliferative response than intradermal.
- A proliferative response could be detected in all lymph tissues tested: spleen, PBMC, and mesenteric, iliac, and inguinal lymph nodes.

**HXB2 Location** Env**Author Location** gp120**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Gag, gp160, Pol *Adjuvant:* CD86

**Species (MHC)** mouse

**References** Kim *et al.* 1997d

- A gp160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecule CD86, gives an increase in the proliferative responses to gp120 in mice.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen**

**Species (MHC)** human

**References** De Berardinis *et al.* 1997

- Sequences flanking helper T-cell immunogenic domains can be important for immunogenicity.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Rosenberg *et al.* 1997

- A strong proliferative response to p24 and gp160 was found in a healthy long term survivor.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** macaque

**Keywords** Th1, Th2

**References** Kent *et al.* 1997b

- *Macaca nemestrina* can be infected with HIV, and clear the infection within 6 months, so it is of interest to examine their initial immune response.
- A strong proliferative response against gp160 with IL-4 production, indicating a Th2 response, was found with 4 weeks of infection.
- The gp160 proliferative response by 8 weeks produces both IL-4 and  $\gamma$  interferon, indicating both Th1 and Th2 responses.

**HXB2 Location** Env

**Author Location** gp120 (HXBc2)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA prime with gp160 boost  
*Strain:* B clade HXBc2 *HIV component:* gp160

**Species (MHC)** macaque

**References** Letvin *et al.* 1997

- Vaccination of *Macaca mulatta* (rhesus monkeys) with a HXBc2 env DNA prime and a protein boost elicited a T-cell proliferative response, a CTL response, and type-specific neutralizing antibodies.
- Vaccinated animals challenged with SHIV-HXB2 were protected from infection.

**HXB2 Location** Env

**Author Location** gp120 (MN)

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA *Strain:* B clade MN

*HIV component:* Env, Rev

**Species (MHC)** human

**References** MacGregor *et al.* 1998

- An HIV DNA env and rev vaccine given to 15 asymptomatic HIV+ individuals at three different dosages, 30, 100 or 300  $\mu$ g, was safe.
- All three groups showed an increased proliferative response after vaccination.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen**

**Species (MHC)** human

**References** Mazzoli *et al.* 1997

- Study of HIV-specific immunity in seronegative partners of HIV-positive individuals – Env peptides could stimulate IL-2 production in 9/16 HIV-exposed seronegative individuals, and only 1/50 low-risk controls.
- Exposed-uninfected produced more IL-2 and less IL-10 than HIV-infected individuals.
- 8/9 of those whose PBMC produce IL-2 in response to Env peptides had concomitantly detected urinary or vaginal tract anti-HIV IgA.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART

**References** Plana *et al.* 1998

- Patients from later stages of infection given HAART do not show restoration of HIV-1 specific Th proliferative responses.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART

**References** Kelleher *et al.* 1998a

- Env and gag Th epitopes were pooled and used to test Th proliferative responses after IL2 therapy – while IL2 therapy causes an increase in CD4+ lymphocyte count, it does not increase HIV-1 specific proliferative responses.

**HXB2 Location** Env

**Author Location** gp160

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein *HIV component:* gp160

**Species (MHC)** human

**References** Ratto-Kim *et al.* 1999

- Vaccinations with rgp160 did not enhance Th immunoproliferative responses in individuals who were immunized every 2 months for 5 years starting early in infection.

**HXB2 Location** Env

**Author Location** gp160

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein *HIV component:* gp160

**Species (MHC)** human

**Keywords** subtype comparisons

**References** Leandersson *et al.* 2000

- 27 HIV subtype B, 4 subtype C, 2 D and one of each subtype E, F, G infected individuals were either given rgp160 B clade immunizations or placebo. All rgp160 immunized individuals showed increased proliferation responses to the B clade immunizing antigen rgp160.
- gp120 was prepared from A, B, C, D, and E subtype virions and used as antigenic stimulus – 7 of 10 tested individuals responded to native gp120 from at least one additional subtype in addition to B subtype, while a placebo recipient did not respond to any gp120.
- This study shows that cross-subtype HIV-specific T-cell proliferative responses can be stimulated in patients already infected with another HIV-1 subtype – all immunized subjects could respond to the subtype B immunogen, but many developed responses to at least one more subtype.

**HXB2 Location** Env

**Author Location** gp160 (MN)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* gp160 prime with gp120 boost  
*Strain:* B clade MN *HIV component:* gp120, gp160

**Species (MHC)** human

**Keywords** Th1, Th2

**References** Gorse *et al.* 1999a

- Helper T-cell memory responses were induced by MN rgp160 as measured by proliferation and Th1 and Th2 cytokine release – this response could be boosted by MN rgp120.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** vaccine

*Vector/Type:* fowlpoxvirus, ISCOM  
*Strain:* B clade SF2 *HIV component:* gp120

**Species (MHC)** macaque

**Keywords** Th1, Th2

**References** Heeney *et al.* 1998b

- Vaccinated monkeys with the highest level of Th1 and Th2 responses and the highest levels of NAbs were protected against a SHIV SF13 challenge – the ISCOM strategy gave more potent anti-gp120 responses than the Fowl pox strategy.
- When animals were challenged 4 months after boost, those that maintained high levels of HIV-1 specific IFN- $\gamma$  responses, indicative of a Th 1 response, were still protected.

**HXB2 Location** Env

**Author Location** (IIIB)

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA *Strain:* B clade IIIB

*HIV component:* Env, Rev

**Species (MHC)** human

**References** Boyer *et al.* 1999

- A DNA vaccine containing env and rev was tested for safety and immune response in 15 HIV+ asymptomatic individuals.
- Enhanced proliferative activity and higher levels of MIP-1 alpha were detected in multiple study subjects.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* gp160 *Adjuvant:* GM-CSF/ENV chimera

**Species (MHC)** mouse

**References** Rodríguez *et al.* 1999

- A chimeric GM-CSF-env antigen expressed in a vaccinia vector elicits a higher HIV-specific env cellular immune response than when native env is used.

**HXB2 Location** Env

**Author Location** Env (LAI)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost

*Strain:* B clade LAI *HIV component:* Env, Gag

**Species (MHC)** macaque

**Keywords** Th1, Th2

**References** Kent *et al.* 1998

- Priming with an HIV-DNA vaccine and boosting with a vaccinia construct induced greater levels of HIV T-cell immunity than either vaccine alone.
- The proliferative response to Env and Gag after the DNA vaccination had a mean SI of 1.5-4, but after boosting with rHIV-fowlpox virus, there was a 6-17 fold increase in the mean SI for HIV Gag and Env. The T help response happened despite a fall in antibody titers, suggesting that the Th response was primarily Th1, not Th2. The CTL response was also enhanced.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA, protein, virus-like particle (VLP), ISCOM

**Species (MHC)** macaque

**Keywords** Th1, Th2

**References** Heeney *et al.* 1999



- Ten different vaccine strategies were evaluated for their ability to protect from infection in a rhesus macaque model using a non-pathogenic SHIV challenge. Protection correlated with the magnitude of NAb responses, beta-chemokines, and a balanced Th response. DNA, protein+adjuvant, VLP and ISCOM vaccines were tested.
- HIV-1/ISCOMS gave the highest NAb titers, Th1 and Th2 responses, was the only vaccine formulation tested with a detectable CTL response, and gave enhanced beta-chemokine production.

**HXB2 Location** Env**Author Location** gp160 (MN)**Epitope****Immunogen** HIV-1 infection, vaccine*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp160**Species (MHC)** human**References** Kundu *et al.* 1998a

- This study followed 10 HLA-A2 asymptomatic HIV+ individuals as they received MN gp160 vaccinations over a two year period.
- There was an increased lymphoproliferative response but this did not impact viral load or CTL response.

**HXB2 Location** Env**Author Location** gp120 (SF2)**Epitope****Immunogen** vaccine*Vector/Type:* DNA, protein, ISCOM  
*Strain:* B clade SF2 *HIV component:* gp120  
*Adjuvant:* MF59**Species (MHC)** macaque**References** Verschoor *et al.* 1999

- 16 rhesus Macaques were vaccinated with either an epidermal SF2 gp120 DNA vaccine, rgp120 with a MF59 adjuvant, or rgp120 incorporated into ISCOMs.
- DNA vaccination elicited a weak Th type 1 response and low antibody response, rgp120/MF59 triggered a strong antibody response, and rgp120/ISCOM induced both kinds of Th cells, and a strong humoral response.
- Animals were challenged with SF13 SHIV. Early induction of Th type 1 and type 2 responses with the rgp120/ISCOM vaccine provided the most effective immunity, protecting from infection.

**HXB2 Location** Env**Author Location** Env (MN)**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade MN  
*HIV component:* Env, Gag, Pol *Adjuvant:* CD80, CD86**Species (MHC)** mouse**References** Kim *et al.* 1998

- Co-stimulatory molecules co-expressed with an HIV-1 immunogen in a DNA vaccine used to enhance the immune response – co-expression of CD86, but not CD80, dramatically increased both HIV Env and Gag/Pol specific CTL and Th proliferative responses.

**HXB2 Location** Env**Author Location** Env (LAI, MN)**Epitope****Immunogen** vaccine*Vector/Type:* canarypox *Strain:* B clade LAI, B clade MN *HIV component:* Gag, gp120, gp41, Protease**Species (MHC)** human**References** Salmon-Ceron *et al.* 1999

- A live attenuated canarypox vector expressing MN gp120 and LAI gp41/gag/protease could induce CTL and a lymphoproliferative response in healthy uninfected volunteers.

**HXB2 Location** Env**Author Location** Env**Epitope****Immunogen** vaccine*Vector/Type:* DNA *Strain:* ZF1 *HIV component:* complete genome**Species (MHC)** macaque**References** Akahata *et al.* 2000

- Rhesus macaques were vaccinated by i.m. injection with naked plasmid DNA carrying an HIV-1 complete genome vaccine, strain ZF1, with a mutated zinc finger in the nucleocapsid to prevent packaging.
- Env and Gag specific CTL but no antibody responses were induced in 2/4 vaccinated monkeys (MM145 and MM153)
- 2/4 monkeys (MM146 and MM143) produced antibodies against p24 and/or gp160, but no CTL response was detected.
- PBMC from all vaccinated monkeys produced IFN- $\gamma$ , in response to HIV-1 gp160, indicating a Th response – this response was 5 times higher in MM145, the animal with the strongest CTL response.
- 4 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM145 and MM153 (with a homologous Env) decreased to near or below the detection limit.
- 6-8 weeks post-challenge with SHIV NM-3rN plasma viral loads of both MM146 and MM143 decreased near or below the detection limit.

**HXB2 Location** Env**Author Location** gp120 (W6.ID)**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**References** Zhang *et al.* 2001b

- T-helper cell proliferative responses to HIV p24, p55 and gp120 were tested in 27 patients with HIV infection – vigorous responses directed at Gag were detected in ten patients, but an Env specific response was detected in only one patient.

**HXB2 Location** Env**Author Location** gp160**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART**References** Blazevic *et al.* 2000

- Prolonged viral suppression resulting from potent anti-retroviral therapy did not allow an HIV T helper response to p24 or gp160, but Th proliferative responses to influenza, alloantigen, and PHA did develop in many HIV+ patients, and asymptomatic patients had stronger and more frequent Th response recovery than AIDS patients.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** vaccine

*Vector/Type:* canarypox prime with gp120 boost *HIV component:* gp120

**Species (MHC)** human

**Keywords** Th1, Th2

**References** Sabbaj *et al.* 2000

- Proliferative responses in PBMC of uninfected individuals that were vaccinated with canarypox vector expressing HIV-1 antigens (ALVAC-HIV) and boosted with a recombinant gp120 subunit vaccine gave a Th1 and Th2 proliferative response upon stimulation with HIV-1 Env.
- All vaccinees produced IFN- $\gamma$  and IL10, most also produced IL-2, IL-6, IL-4 and IL-5.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein *Strain:* B clade MN *HIV component:* gp120

**Species (MHC)** human

**Keywords** Th1

**References** Hladik *et al.* 2001

- 16/29 HIV-1 infected and 24/30 vaccinated individuals had DTH reactions within 48 hours after an intradermal rec gp120 injection. Of nine DTH positive individuals, none had detectable proliferative responses. Thus skin testing may be a sensitive way to identify people with Th recall responses to vaccines, or in the absence of lymphoproliferation.
- No 48 hour DTH responses were detected among uninfected volunteers, although 10/35 (40%) of the high risk and 11/32 (34%) of the low risk individuals developed an induration resembling DTH after 7-12 days, that may be indicative of primary induction of HIV-1 specific Th1-immunity.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression, Th1, Th2

**References** Wilson *et al.* 2000b

- Dysfunction of HIV-1 specific proliferative responses, but not responses to other antigens, is evident in HIV-1 progressive disease.
- Vigorous HIV-1 specific responses to p24, Nef and gp120 with SI between 8-99 were seen in 6/7 long term non-progressors (LTNP), the seventh had a borderline responses. IL-2 production was seen in all cases, and IL-4 production was also evident many responses.
- None of the progressors (0/5) had HIV-1 specific proliferative responses, or IL-2 or IL-4 induction.
- Non-HIV antigens (cytomegalovirus, PPD, Staphylococcus enterotoxin B, tetanus toxoid) gave similar responses in HIV-1 + LTNP, progressors, and HIV-1 controls.

**HXB2 Location** Env

**Author Location** gp160

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression, Th1

**References** Kalams *et al.* 1999a

- The strength of p24 specific Gag proliferative responses (SIs) were inversely correlated with viral load in 21 ARV naive patients. The responses were Th1, IFN $\gamma$  producing.
- Proliferative responses against gp160 were rarely observed (only 4 cases).

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor  
*Strain:* B clade MN *HIV component:* Env, Rev  
*Adjuvant:* Bupivacaine

**Species (MHC)** human

**Keywords** early-expressed proteins

**References** MacGregor *et al.* 2002

- A phase I clinical trial of a HIV-1 Env and Rev DNA vaccine with a CMV promoter was conducted and Th proliferative, CTL and Elispot responses monitored. The construct was modified for safety and included no LTRs or packaging signals. The vaccine strategy was safe, and elicited strong CD4-T cell responses, but not CD8 T-cell responses. Rev elicited strong Th responses, and is a early produced protein so may confer advantages.
- With a 300 ug dose, 4/6 individuals had a lymphocyte proliferation (LP) responses to gp120, 3/6 to Rev.
- With a 1000 ug dose, 4/6 individuals had a LP and 2/6 had IFN $\gamma$  Elispot responses to gp160; 3/6 had LP, and 4/6 had IFN $\gamma$  Elispot responses to Rev.

- No responses to three specific CTL epitopes were observed by Elispot in individuals with appropriate HLA. Some cytotoxic activity against whole protein was observed that was CD4+ T-cell mediated.

**HXB2 Location** Env

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART

**References** Clerici *et al.* 2002b

- Specific immunity was compared in a two-year study of chronically HIV-1 infected i) HAART-naïve patients who were not progressing and had strong immune responses, ii) newly treated patients followed for 24 months after initiation of HAART, iii) and long-term HAART patients who had been on HAART at least 12 months prior to the study.
- HAART naïve patients had strongest proliferative responses at time zero, but long-term HAART patients the most significant increase in specific responses over the two year study period against HIV-1 gp160, influenza, and *Candida*. Similarly, IL-2 and IFN- $\gamma$  production in responses to gp160 was highest in the naïve group at time zero, but increased the most in the long-term HAART treated patients.
- Short-term HAART patients showed a significant improvement in their CD4+ T cell count and a reduction of plasma viremia, and had augmented IL-7 production, which was slightly reduced in long-term HAART patients.

**HXB2 Location** Env

**Author Location** gp160

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART

**References** Palmer *et al.* 2002

- CD4+ T cell proliferative responses from 33 HIV-1 infected patients with HAART suppression were compared to 19 patients with active viral replication (HAART failures and HAART naïve). Patients with HAART suppression showed stronger p24- and p66-specific proliferative responses compared to patient groups with active HIV-1 replication, suggesting active viral replication *in vivo* specifically reduces proliferation responses.
- gp160 proliferation responses were apparent in 7/32 donors tested, but weaker overall, with a median value for the suppressed group not above that found for HIV seronegative controls.
- No differences in the frequency of HIV-specific CD4+ T-cells that were positive for cytokine secretion in a flow cytometry assay were found in the HAART suppressed group versus the group with active viral replication.

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
- After 12 months, most responses were lost or diminished, and specific responses fluctuated. 4/10 of the responders at baseline had new responses at 12 months, as did 5/15 non-responders.
- IL-2 production was a more sensitive and well-preserved measure of Th function than proliferation.
- 4/15 responders recognized this peptide, average SI = 4.4.

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Geretti *et al.* 1994

- Th proliferative responses were studied in 36 asymptomatic HIV-1 + patients. PBMC from 15/36 patients responded to stimulation with gp120 synthetic overlapping peptide pools. 10 of the responding patients recognized three or more peptide pools.
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- 4/15 responders recognized this peptide, average SI = 4.4.

**HXB2 Location** Env

**Author Location** gp120 (SF2)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons, rate of progression

**References** Imami *et al.* 2002b

- 70 patients with chronic disease progression, 10 clinical non-progressors, and 3 immunologically discordant progressors (individuals who controlled viremia but had progressive CD4+ T-cell decline) were analyzed for their T-helper cell responses to p24 and cytokine profile.
- In a comparison of responses to HIV-1 proteins based on 10 non-progressors, 3 immunologically discordant, and 70 progressors, SIs were always much higher for non-progressors and immunologically discordant than progressors. Among the non-progressors, the responses to different antigens were greater using p24 peptides than native p24. Native p24, Nef, gp120 proteins, and Remune (gp120 depleted HIV-1, p24 is subtype G), had roughly comparable distributions of SI values from the non-progressors, Nef and gp120 responses were somewhat diminished in immunologically discordant patients.

**HXB2 Location** Env

**Author Location** (BRU)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* B clade BRU *HIV component:* virus *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse**References** Haas *et al.* 1991

- Of 5 mouse inbred lines tested: DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.
- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.

**HXB2 Location** Env**Author Location** gp120 (HIV-1,IIIB)**Epitope****Immunogen** HIV-1 exposed seronegative**Species (MHC)** human**Assay type** Cytokine production**Keywords** HIV exposed persistently seronegative (HEPS)**References** Fowke *et al.* 2000

- A cohort of Nairobi sex-workers were defined to be resistant to infection by virtue of remaining seronegative despite repeated high risk exposure. 24 were tested for HIV specific T-helper responses determined by IL-2 production *in vitro* in response to gp120 peptides or soluble gp120 protein.
- In 7/17 resistant women showed IL-2 stimulation  $\geq 2.0$ , and specific CTL responses were detected in 15/22 resistant women. 0/12 of the control low-risk subjects had detectable T-cell responses.

**HXB2 Location** Env**Author Location** gp160**Epitope****Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein *HIV component:* gp160 *Adjuvant:* aluminum phosphate

**Species (MHC)** human**Assay type** proliferation**Keywords** HAART, ART, immunotherapy**References** Hejdeman *et al.* 2003

- Groups of ten asymptomatic HAART-treated HIV-1 + patients with undetected viral loads were monitored for two years after i) no immunization, ii) immunization with rgp160, or iii) immunization with tetanus. Ten HIV-1- volunteers were immunized with tetanus as a control. Results were compared with an rgp160 group tested before HAART was available. The HAART-treated group had increased magnitude and duration of proliferative response to rgp160, maintaining the response for the two year study period. CD4 T-cell responses to tetanus were also improved in the HAART group.
- The recall response to tetanus toxoid and tuberculin were boosted by the rgp160 immunization, particularly in the HAART-treated group.

**HXB2 Location** Env**Author Location****Epitope****Immunogen** HIV-1 exposed seronegative**Species (MHC)****Assay type** Cytokine production**Keywords** HIV exposed persistently seronegative (HEPS), acute/early infection, early treatment**References** Puro *et al.* 2000

- This was a case report of a health care worker who had an percutaneous injury and exposure to HIV, and was immediately given combination therapy. The individual remained HIV Ab negative, but had transiently detectable viral RNA 2-3 weeks after the exposure. 58 weeks after exposure a Th response was detected by IL-2 production in response to HIV Env peptides.

**HXB2 Location** Env**Author Location****Epitope****Immunogen** vaccine

*Vector/Type:* fowlpoxvirus, DNA prime with virus-like particle (VLP) boost *Strain:* B clade 89.6 *HIV component:* Env, Gag-Pol

**Species (MHC)** rabbit**Assay type** Cytokine production**Keywords** Th1, Th2**References** Radaelli *et al.* 2003

- Rabbits were immunized with fowlpox recombinant vectors or expression plasmids, which express either SIVmac239 gag/pol or HIV-1 env 89.6P genes, and then boosted with virus-like particles (VLPs)(gag/pol SIV with HIV env 89.6).
- A lymphoproliferative Th0 profile response and homologous neutralizing Ab were seen in all three groups. The pcDNA3gag/pol SIV construct was more efficient at producing Abs than the fowlpox construct, although the fowlpox env89.6 construct elicited good humoral and cellular responses. VLP boosting was shown to be efficacious; the pseudoviral structure of the VLP providing a more natural protein conformational was considered helpful for eliciting long term memory cells.

**HXB2 Location** Env**Author Location** gp160**Epitope****Subtype** B**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* canarypox prime with gp160 boost *Strain:* B clade MN/LAI-2 *HIV component:* gp160

**Species (MHC)** human**Assay type** proliferation**Keywords** vaccine-specific epitope characteristics, vaccine-induced epitopes**References** Ratto-Kim *et al.* 2003

- The CD4+ T-helper response to vaccinees given ALVAC-HIV(vCP205) alone, rgp160 MN/LAI-2 alone, or the two combined in a prime-boost was investigated by establishing T cell lines and comparing proliferative responses to a series of peptides (15 mers overlapping by 10) spanning autologous gp160 MN/LAI-2. Th responses against Env during natural HIV-1 infection were also studied.

- Broad, strong T-helper responses scattered across the Env were obtained from volunteers who received a prime boost vCP205 + rgp160MN/LAI-2, while those receiving rgp160 responded to fewer peptides, and vCP205 to very few peptides.
- HIV-1 + volunteers had less breadth and amplitude of Th responses than vaccinees that got the prime-boost vaccine, although T-cell lines were readily generated from HIV+ individuals. Some vaccinees targeted C1 and C5, while infected individuals did not, and some infected individuals targeted V3, while vaccinees did not.
- The authors note that the differences in response may be contributed to by the fact the peptides used to screen the responses were the same as the vaccine strain, and different than the strains in the natural infection, but that there also may be real immunological differences in the two scenarios of vaccine versus natural infection.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)**

**Assay type** proliferation

**Keywords** HAART, ART

**References** Sullivan *et al.* 2003

- Lymphoproliferative responses to HIV antigens p24, gp120 and Nef were enhanced in eight patients who were switched from protease inhibitors to non-nucleoside reverse transcriptase inhibitors.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** Cytokine production, proliferation

**Keywords** HAART, ART

**References** Hardy *et al.* 2003

- Upon initiating HAART, CD4+ T cell proliferative responses in 36 patients were restored to specific antigens, mitogens, and IL-2. Restored recall responses were largely to persistent antigens, and not to HIV-1 or new antigens, and recall responses were associated with IL-2, not IL-4 production.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** review, Th1, Th2, immune dysfunction

**References** Becker 2004b

- The review suggests HIV-1 shed gp120 virions can act as an allergen, inducing Th2 cytokine production, in particular IL-4, by Fc epsilon RI+ hematopoietic cells. This could inhibit IgG production and CTL responses, and inactivate Th1 cells. New vaccination strategies employing IL-4 inhibitors and anti-allergen drugs are discussed.

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** review, Th1, Th2, immune dysfunction

**References** Becker 2004a

- Review raises the possibility that the switch from Th1 to Th2 activity along with an increase in IL-4 and IgE production in HIV-1 infected patients are an allergic response to HIV-1 protein gp120. Alternative treatments to block Th2 cytokine production, e.g. with IL-4 receptor inhibitors, are discussed.

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* peptide, heat-shock protein (HSP70) *Strain:* B clade IIIB *HIV component:* gp120

**Species (MHC)** macaque

**Assay type** Cytokine production, proliferation, CD4 T-cell Elispot - IFN $\gamma$ , T-cell Elispot

**Keywords** genital and mucosal immunity, vaccine antigen design

**References** Bogers *et al.* 2004

- Macaques were given vaginal or iliac lymph node immunizations with a novel peptide vaccine composed of SIV p27, CCR5, and N-terminal gp120 fragment, and hsp70 as a carrier.
- 5/8 SHIV 89.6P challenged macaques were protected from infection and vaccinated animals had higher CD4+ T cell numbers than non-vaccinated controls. T-cell proliferation in responses to gp120, vaginal IgG and IgA Abs, and cells producing IL-2, IL-4, and IFN $\gamma$  were increased in vaccinated animals.

**HXB2 Location** Env

**Author Location** gp160 (IIIB)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA, protein, baculovirus *Strain:* B clade IIIB *HIV component:* gp160, Nef, Rev, Tat *Adjuvant:* aluminum phosphate

**Species (MHC)** human

**Country** Sweden

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$

**Keywords** HAART, ART, subtype comparisons, supervised treatment interruptions (STI), immunotherapy

**References** Boström *et al.* 2004

- In this study, HIV-infected patients who had previously been immunized with DNA plasmid (nef, tat and rev) or recombinant gp160 were followed longitudinally to determine the impact of HAART on specific T-cell responses. While therapeutic immunizations had transient effects on CD4 cell counts, there was increased survival at 2 years.

- After gp160 vaccination, gp160-specific proliferative CD4+ T cell responses to both baculovirus (MGS HIV-1 rgp 160) and to IMMUNO AG derived gp160 were increased, as well as to p24. Long term HAART treatment was associated with increased IFN- $\gamma$  producing T-cells.
- T-cell proliferative responses to gp160 vaccination were maintained for up to 7 years.

**HXB2 Location** Env

**Author Location** Env (HXB2. BaL)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade 1007

*HIV component:* Env, Gag-Pol, Nef

**Species (MHC)** macaque

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , T-cell Elispot

**Keywords** variant cross-recognition or cross-neutralization, co-receptor

**References** Letvin *et al.* 2004

- SIVmac239 gag-pol-nef vaccination of macaques confers better protective responses against a SHIV 89.6 challenge if Env is included even when the vaccine and challenge strain were heterologous in Env. This protection, realized by decreased viral replication and higher levels of CD4+ T cells over time, was associated with T-cell responses early in infection, but not neutralizing Abs.
- The 24 Indian-origin rhesus macaques included in this study did not express Mamu-A\*01.

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** CRF02\_AG

**Immunogen** HIV-1 or HIV-2 infection

**Species (MHC)** human

**Country** Senegal

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** rate of progression, variant cross-recognition or cross-neutralization

**References** Zheng *et al.* 2004

- Gag, Env, Tat, and Nef-specific T-cell responses were evaluated in 68 HIV-1 and 55 HIV-2 infected drug naive, generally asymptomatic, infected Senegalese patients.
- HIV-1 peptides were derived from HIV-1 CRF-02 (HIV-1 A/G, AJ251056) and HIV-2 peptides spanning HIV-2 ROD (M15390).
- Gag specific responses dominated in both groups, but overall magnitude and frequencies did not correlate with viral load or CD4 counts. More Nef responses were found in HIV-1 infected people than HIV-2, and Nef in HIV-2 is more diverse.

**HXB2 Location** Env

**Author Location**

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor

*Strain:* B clade HXB2, B clade NL43, A clade 92RW020, C clade 97ZA012 *HIV component:* Env, Gag, Nef, Pol

**Species (MHC)** human

**Country** United States

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Flow cytometric T-cell cytokine assay

**Keywords** therapeutic vaccine

**References** Catanzaro *et al.* 2006

- 14 volunteers uninfected with HIV completed a set of injections with a 6-plasmid DNA vaccine encoding EnvA, EnvB, EnvC, and subtype B Gag, Pol, and Nef. CD4 and CD8 T cell responses to Env and Gag were most frequently detected.
- For EnvA, 11/14 subjects showed a positive CD4+ T cell response by ICS.

**HXB2 Location** Env

**Author Location**

**Epitope**

**Immunogen** vaccine

*Vector/Type:* adenovirus type 5 (Ad5) *HIV*

*component:* Env, Gag *Adjuvant:* Cholera toxin (CT)

**Species (MHC)** macaque

**Assay type** proliferation, CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, Other

**Keywords** vaccine antigen design

**References** Mercier *et al.* 2007

- 3 rhesus macaques were given oral immunizations with an enteric-coated mixture of adenoviral vectors expressing HIV-1 gag and a string of conserved env peptides representing broadly cross-reactive CD4+ and CD8+ epitopes. The macaques were boosted intranasally with a mixture of 6 HIV-1 envelope peptides plus cholera toxin adjuvant.
- The immunizations increased cellular immune responses, including antigen-specific IFN $\gamma$ -producing CD4+ and CD8+ effector memory T cells in the intestine. After only the oral immunization, there were no EliSpot responses to env peptides or to gag. After the intranasal boost, EliSpot responses against env peptides and against inactivated HIV were markedly increased, but gag responses were not.

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA prime with vaccinia boost

*Strain:* B clade JRFL, A clade 92RW020, M group Consensus, C clade 96ZM651 *HIV component:* Env

**Species (MHC)** mouse

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$

**Keywords** variant cross-recognition or cross-neutralization, vaccine antigen design

**References** Weaver *et al.* 2006

- 3 different mouse strains were immunized with subtype A, B, C, and M-group consensus env DNA immunogens. CTL and Helper T-cell epitopes were mapped using peptide sets from heterologous A, B, and C viruses. The consensus immunogen

induced a greater number and magnitude of T-cell responses than any single wild-type env.

**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* B clade  
**Species (MHC)** macaque  
**Assay type** Intracellular cytokine staining  
**Keywords** subtype comparisons, vaccine antigen design  
**References** Smith *et al.* 2005

- Macaques were immunized with a clade B HIV vaccine and tested for responses to pools of clade B and A/G Env and Gag peptides. While CD4 responses were more frequent than CD8 responses, higher cross-clade responses were found for CD8 responses. The authors suggest that the better cross-clade reactivity of the CD8 responses reflects the size difference between CD8 and CD4 epitopes; the smaller CD8 epitopes provide a smaller target for mutation.
- All 5 pools of B Env and Gag peptides stimulated CD4 responses, while only 2 pools of A/G peptides stimulated responses, suggesting that 1 or 2 out of 5 CD4 epitopes were cross-reactive.

**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* Other  
*HIV component:* Env, Gag, Pol, Rev, Tat, Vif, Vpr  
**Species (MHC)** macaque  
**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , Tetramer binding, CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining  
**Keywords** vaccine-induced epitopes, vaccine antigen design  
**References** Sadagopal *et al.* 2005

- 22/23 macaques that were immunized with a DNA prime SHIV-89.6 and boosted with rMVA showed successful control of viremia, with low or undetectable viral loads and normal CD4 counts 200 weeks postchallenge. IFN-gamma producing T cells were found in unexpectedly low breadths and frequencies. T-cell responses were stable over time and maintained their production of IFN-gamma and IL-2. Long-term control was found in macaques of diverse histocompatibility types. The CD8 T cells seemed to have the most impact on well-contained chronic infections in the vaccinated and challenged animals.
- After challenge, vaccinated animals maintained normal levels of CD4 cells, while unvaccinated animals quickly lost CD4 cells. Both CD4 and CD8 responses were found to the SIV Gag and HIV Env proteins; 60% of CD8+ epitopes and 80% of CD4+ epitopes were in p27.

### III-B-18 Nef Helper/CD4+ T-cell epitopes

**HXB2 Location** Nef (1–20)  
**Author Location** Nef (1–20 LAI)  
**Epitope** MGGKWSKSSVVGWPTVRERM  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade LAI  
*HIV component:* Nef, Rev, Tat  
**Species (MHC)** mouse (H-2<sup>d</sup>)  
**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (1–20)  
**Author Location** Nef (1–20 HXB2)  
**Epitope** MGGKWSKSSVIGWPTVRERM  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** (H-2<sup>d</sup>)  
**Keywords** class I down-regulation by Nef  
**References** Peng & Robert-Guroff 2001

- Deletion of the 19 N-terminal amino acids from Nef including the myristolation signal eliminates Nef-induced down-regulation of MHC class I and CD4 molecules. Such a construct has the potential to serve as a more potent immunogen. The known T-cell epitopes that would be disputed by this deletion are minimal, a murine H-2d Th epitope in the peptide MGGKWSKSSVIGWPTVRERM, and a HLA-B8 CTL epitope, WPTVRERM.

**HXB2 Location** Nef (8–23)  
**Author Location** (clade B consensus)  
**Epitope** RSVVGWPAVRERMRRR  
**Subtype** B  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Donor MHC** A\*0101, A\*0201, B\*0801, B\*1302, Cw\*0602, Cw\*0701, DRB1\*0301  
**Country** United States  
**Assay type** CD4 T-cell Elispot - IFN $\gamma$   
**Keywords** escape  
**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- ckmsGWsnVRERMRRR variant coincided with a positive response. ckmsGWsnVREkMRRR variant 5 weeks later coincided with no response.

**HXB2 Location** Nef (14–22)  
**Author Location** Nef (14–22 SF2)  
**Epitope** SAIRERMRR  
**Epitope name** 95.12, 33.6  
**Subtype** B  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (DRw6)

**Donor MHC** DP4, DQw1, DQw6, DRw15(2), DRw52, DRw6

**Assay type** proliferation

**Keywords** epitope processing

**References** Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.
- The two clones that recognized the epitope SAIRERMRR could also auto-present Nef protein, suggesting that they recognized this epitope in the context of the intact, unprocessed protein.

**HXB2 Location** Nef (14–30)

**Author Location** (clade B consensus)

**Epitope** PAVRERMRRRAEPAADGV

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0101, A\*0201, B\*0801, B\*1302, Cw\*0602, Cw\*0701, DRB1\*0301; A\*0101, A\*0201, B\*4001, C\*0304, DRB1\*0801, DRB1\*1301

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- In one patient, snVRERMRRtEPAADGV variant coincided with a positive response. snVREkMRRtEPAADGV variant 5 weeks later coincided with no response. In another patient, PkVRERMkqAEPAADGV variant coincided with a positive response. PkVRERMkqAEPAAAnGV variant 4 weeks later coincided with very diminished response.

**HXB2 Location** Nef (16–35)

**Author Location** Nef (16–35 LAI)

**Epitope** VRERMRRRAEPAADGVGAASR

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (21–37)

**Author Location** (clade B consensus)

**Epitope** RRAEPAADGVGAVSRDL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0101, A\*0201, B\*4001, C\*0304, DRB1\*0801, DRB1\*1301

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- kqAEPAAADGVGAVSqDL variant coincided with low response. kqAEPAAAnGVGAVSqDL variant 4 weeks later coincided with an increased response.

**HXB2 Location** Nef (31–50)

**Author Location** Nef (31–50 LAI)

**Epitope** GAASRDLEKHGAISSNTAA

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (37–51)

**Author Location**

**Epitope** LEKHGAISSNTAAT

**Epitope name** N010

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada

**Assay type** proliferation, Flow cytometric T-cell cytokine assay

**Keywords** memory cells

**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** Nef (37–51)

**Author Location**

**Epitope** LEKHGAISSNTAAT

**Epitope name** N010

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada



- Assay type** proliferation, Flow cytometric T-cell cytokine assay
- Keywords** memory cells
- References** Younes *et al.* 2003
- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
  - CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.
- HXB2 Location** Nef (43–49)
- Author Location** Nef (47–53 SF2)
- Epitope** ITSSNTA
- Epitope name** I.13
- Subtype** B
- Immunogen** *in vitro* stimulation or selection
- Species (MHC)** human (DQw7)
- Donor MHC** DP4, DQw1, DQw7, DR1, DR8, DRw52
- Assay type** proliferation
- Keywords** epitope processing
- References** Wentworth & Steimer 1994
- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
  - These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.
- HXB2 Location** Nef (45–59)
- Author Location**
- Epitope** SSNTAATNAACAWLE
- Epitope name** N012
- Immunogen** HIV-1 infection
- Species (MHC)** human
- Country** Canada
- Assay type** proliferation, Flow cytometric T-cell cytokine assay
- Keywords** memory cells
- References** Younes *et al.* 2003
- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
  - CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.
- HXB2 Location** Nef (45–69)
- Author Location** Nef (45–69 BRU)
- Epitope** SSNTAATNAACAWLEAQEEEEVGFP
- Immunogen** vaccine
- Vector/Type:** peptide prime with protein boost
- Strain:** B clade BRU
- HIV component:** Nef
- Species (MHC)** chimpanzee, rat
- References** Estaquier *et al.* 1992
- Antigenic domain: ATNAACAWL, priming with peptide enhanced subsequent Ab response to Nef protein immunization.
- HXB2 Location** Nef (45–69)
- Author Location** Nef (45–69)
- Epitope** SSNTAATNAACAWLEAQEEEEVGFP
- Immunogen** vaccine
- Vector/Type:** peptide
- Adjuvant:** aluminum hydroxide
- Species (MHC)** rat
- Keywords** vaccine-specific epitope characteristics
- References** Rouaix *et al.* 1994
- Covalently linking the potent Th epitope Nef 45-69, which can induce Th proliferative responses at low doses with no adjuvant in Lou/M rats, to a weaker epitope from *Schistosoma mansoni* allows the induction of detectable Th responses to the *Schistosoma* epitope.
- HXB2 Location** Nef (46–65)
- Author Location** Nef (46–65 LAI)
- Epitope** SNTAATNAACAWLEAQEEEE
- Subtype** B
- Immunogen** vaccine
- Vector/Type:** DNA
- Strain:** B clade LAI
- HIV component:** Nef, Rev, Tat
- Species (MHC)** mouse (H-2<sup>d</sup>)
- References** Hinkula *et al.* 1997
- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
  - Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.
- HXB2 Location** Nef (56–68)
- Author Location** Nef (56–68)
- Epitope** AWLEAQEEEEVGFP
- Epitope name** Nef-4
- Immunogen** HIV-1 infection
- Species (MHC)** human (DQ)
- Country** France
- Assay type** proliferation
- Keywords** computational epitope prediction, cross-presentation by different HLA
- References** Pancré *et al.* 2007
- Responses to 4 Nef epitopes (3 HLA-DR epitopes selected with TEPITOPE software and 1 HLA-DQ epitope) were evaluated in treatment naive asymptomatic patients and long term non-progressors. 2 years later, more than half medium- and non-responders followed bi-therapy, while high responders to Nef peptides still were without antiretroviral treatment and conserved stable CD4 counts, indicating that Nef specific CD4+ response is associated with non-progression.
  - Proliferative response to Nef epitopes was always associated with high IFN- $\gamma$  secretion.

- AWLEAQEEEEVGF was described as promiscuous HLA-DQ epitope in Pancre2002.

**HXB2 Location** Nef (56–68)  
**Author Location** Nef (56–68 HXB2)  
**Epitope** AWLEAQEEEEVGF  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* Nef  
*Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (MHC)** mouse (DQ2, DQ3, DQ5, DQ6, DQ7, DQ8)  
**Keywords** binding affinity, cross-presentation by different HLA, Th1, TCR usage  
**References** Pancré *et al.* 2002

- This highly conserved Nef epitope has promiscuous HLA-DQ class II binding potential. It has a can bind to 6 different HLA-DQ alleles, but did not bind to any HLA-DR alleles tested. It bound to DQ2 and DQ8 with particularly high affinity, and with DQ7 with low affinity.
- DQ transgenic mice (in particular DQ8) mounted strong cellular and humoral responses after immunization with this peptide.
- Ex vivo stimulation of CD4+ T-cells from 14 healthy donors (with diverse HLAs) with this peptide presented on autologous DCs resulted in Th1-associated cytokine production. IFN $\gamma$  production was stimulated in 7/14 cases, both IFN $\gamma$  and IL-2 in 6/14, and just IL-2 in 1/14. No IL-4 or IL-5 production was observed.
- Peptide-specific CD4+ T-cell clones with different HLA presenting molecules demonstrated a preference for TCR V $\beta$ 6.1.

**HXB2 Location** Nef (56–68)  
**Author Location** Nef (56–68)  
**Epitope** AWLEAQEEEEVGF  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade *HIV component:* Nef  
**Species (MHC)** transgenic mouse (DQ6, DQ8)  
**Assay type** proliferation, HLA binding  
**Keywords** binding affinity, computational epitope prediction  
**References** Depil *et al.* 2006

- A combination of peptide-binding assays and HLA II transgenic mice experiments was suggested for selecting T helper epitopes. HIV Nef peptide AWLEAQEEEEVGF and Sm28GST peptide ENLLASSPRLAKYLSNRPATPF were used as models.

**HXB2 Location** Nef (61–80)  
**Author Location** Nef (61–80 LAI)  
**Epitope** QEEEEVGFVTPQVPLRPMT  
**Subtype** B  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade LAI  
*HIV component:* Nef, Rev, Tat  
**Species (MHC)** mouse (H-2<sup>b</sup>)  
**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.

- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (64–73)  
**Author Location** Nef (68–77 SF2)  
**Epitope** EEVGFVVRPQ  
**Epitope name** 59.25  
**Subtype** B  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (DRw15(2))  
**Donor MHC** DP4, DQw1, DR1, DRw15(2)  
**Assay type** proliferation  
**Keywords** epitope processing  
**References** Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.

**HXB2 Location** Nef (65–79)  
**Author Location**  
**Epitope** EVGFVPIQVPLRPM  
**Epitope name** N017  
**Immunogen** HIV-1 infection  
**Species (MHC)** human  
**Country** Canada  
**Assay type** proliferation, Flow cytometric T-cell cytokine assay  
**Keywords** memory cells  
**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** Nef (66–73)  
**Author Location** Nef (70–77 SF2)  
**Epitope** VGFVVRPQ  
**Epitope name** 29.16  
**Subtype** B  
**Immunogen** in vitro stimulation or selection  
**Species (MHC)** human (DR1, DRw15(2))  
**Donor MHC** DP4, DQw1, DR1, DRw15(2)  
**Assay type** proliferation  
**Keywords** epitope processing  
**References** Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.

- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.

**HXB2 Location** Nef (66–88)

**Author Location**

**Epitope** VGFPVPRQVPLRPMTYKAAVDLS

**Epitope name** HIV-VAX-1062

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** subtype comparisons, computational epitope prediction, vaccine antigen design

**References** De Groot *et al.* 2005

- 9-mers conserved across clades were analyzed by computer for affinity to DRB\*0101. 23-mers were synthesized based on these predicted epitopes. 19/20 of these 23-mers were confirmed to be immunogenic in US HIV-infected subjects.
- 5/13 US test subjects responded to this 23-mer by CD4 Elispot assay. The core computer-predicted peptide was QVPLRPMTY.

**HXB2 Location** Nef (66–97)

**Author Location** Nef (66–97)

**Epitope** VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGGL

**Epitope name** Nef-2

**Immunogen** HIV-1 infection

**Species (MHC)** human (DQ)

**Country** France

**Assay type** proliferation

**Keywords** computational epitope prediction, cross-presentation by different HLA

**References** Pancré *et al.* 2007

- Responses to 4 Nef epitopes (3 HLA-DR epitopes selected with TEPITOPE software and 1 HLA-DQ epitope) were evaluated in treatment naïve asymptomatic patients and long term non-progressors. 2 years later, more than half medium- and non-responders followed bi-therapy, while high responders to Nef peptides still were without antiretroviral treatment and conserved stable CD4 counts, indicating that Nef specific CD4+ response is associated with non-progression.
- Proliferative response to Nef epitopes was always associated with high IFN- $\gamma$  secretion.
- VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGGL was predicted by TEPITOPE to bind HLA DR1, DR3, DR4, DR7, DR11, DR15, DRB5.

**HXB2 Location** Nef (66–97)

**Author Location** Nef (66–97 LAI)

**Epitope** VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGGGL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide

**Species (MHC)** human

**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.

- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 5/10 reacted to this Nef peptide.

- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual.

- 5/12 tested had an IgG response to this peptide.

**HXB2 Location** Nef (73–90)

**Author Location** (clade B consensus)

**Epitope** QVPLRPMTYKAAVDLSHF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0201, A\*0205, B\*3501, B\*4901, Cw\*040, Cw\*0701, DRB1\*0101, DRB1\*100101; A\*0201, A\*290201, B\*1501, B\*4403, Cw\*0304, Cw\*1601, DRB1\*0401, DRB1\*0701

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** escape

**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- In one patient, QVPLRPMTYKAAIDLSHF mutation was coincident with a gain of response. In another patient, QVPLRPMTYKgAIDLtHF variant coincided with no response. QVPLRPMTYKgAIDLShf variant 4 weeks later coincided with a positive response.

**HXB2 Location** Nef (76–95)

**Author Location** Nef (76–95 LAI)

**Epitope** LRPMYKAAVDLSHFLKEKG

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>b</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (81–97)

**Author Location** Nef (81–97 B Consensus)

**Epitope** YKAAVDLSHFLKEKGGGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.

**HXB2 Location** Nef (81–97)

**Author Location** (clade B consensus)

**Epitope** YKAAVDLSHFLKEKGGGL

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Donor MHC** A\*0201, A\*290201, B\*1501, B\*4403, Cw\*0304, Cw\*1601, DRB1\*0401, DRB1\*0701

**Country** United States

**Assay type** CD4 T-cell EliSpot - IFN $\gamma$

**Keywords** escape

**References** Rychert *et al.* 2007

- Sequence mutations were studied during acute infection in 7 subjects. Mutations within CD4 epitopes were coincident with changes in the peptide-specific CD4 response.
- YK<sub>g</sub>AIDLtHFLKEKGGGL coincided with no response. YK<sub>g</sub>AIDL<sub>S</sub>HFLKEKGGGL variant 4 weeks later coincided with a positive response.

**HXB2 Location** Nef (91–110)

**Author Location** Nef (91–110 LAI)

**Epitope** LKEKGGLEGLIHSQRRQDIL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>b</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (98–112)

**Author Location** Nef (98–112 BRU)

**Epitope** EGLIHSQRRQDILDL

**Immunogen** vaccine

*Vector/Type:* peptide prime with protein

*boost Strain:* B clade BRU *HIV component:* Nef

**Species (MHC)** chimpanzee

**References** Estaquier *et al.* 1992

- Peptide alone could stimulate monkey T-cells in the absence of carrier protein – required carrier protein in rat.

**HXB2 Location** Nef (104–121)

**Author Location** Nef (104–121 B Consensus)

**Epitope** QKRQDILDLWVYHTQGYF

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell EliSpot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNP's responded to many peptides, comparable to acute STI.

**HXB2 Location** Nef (104–123)

**Author Location** Nef (106–125 HXB3)

**Epitope** QRRQDILDLWIYHTQGYFPD?

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade HXB3

*HIV component:* Nef

**Species (MHC)** mouse (H-2<sup>b</sup>)

**References** Sandberg *et al.* 2000

- A strong T helper proliferative response against a rec Nef protein was observed 2 weeks after immunization of HLA-A201 transgenic mice in a C57Bl/6 background – the response was weak by 4 weeks post immunization.
- Mice were immunized with nef DNA under the control of a CMV promoter, coated on gold particles delivered to abdominal skin by a gene gun.
- Primary responses were directed at peptides 106-125, 166-185, and 181-205, indicating a response to multiple epitopes.

**HXB2 Location** Nef (106–125)

**Author Location** Nef (106–125 LAI)

**Epitope** RQDILDLWYHTQGYFPDQW

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI  
*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>b</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (112–127)

**Author Location** Nef (112–127 B Consensus)

**Epitope** LWVYHTQGYPDWQNY

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** Nef (112–128)

**Author Location** Nef (111–128)

**Epitope** LWVYHTGQGYFPDWQNYT

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Netherlands

**Assay type** Cytokine production

**References** Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.
- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. LWVYHTGQGYFPDWQNYT had fixation of 1 mutation (LWVYHTGQGYFPDW[q/d]NYT) in 1 of the patients.

**HXB2 Location** Nef (117–147)

**Author Location** Nef (117–147 LAI)

**Epitope** TQGYFPDWQNYTPGPGVRYPLTFGWICYLVP

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide

**Species (MHC)** human

**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 1/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual.
- 10/12 tested had an IgG response to this peptide.

**HXB2 Location** Nef (121–140)

**Author Location** Nef (121–140 LAI)

**Epitope** FPDWQNYTPGPGVRYPLTFG

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>b</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (133–159)

**Author Location** Nef (133–159)

**Epitope** VRYPLTFGWICYKLVPEPDKVEEANKG

**Epitope name** Nef-3

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR)

**Country** France

**Assay type** proliferation

**Keywords** computational epitope prediction, cross-presentation by different HLA

**References** Pancré *et al.* 2007

- Responses to 4 Nef epitopes (3 HLA-DR epitopes selected with TEPITOPE software and 1 HLA-DQ epitope) were evaluated in treatment naive asymptomatic patients and long term non-progressors. 2 years later, more than half medium- and non-responders followed bi-therapy, while high responders to Nef peptides still were without antiretroviral treatment and conserved stable CD4 counts, indicating that Nef specific CD4+ response is associated with non-progression.
- Proliferative response to Nef epitopes was always associated with high IFN- $\gamma$  secretion.
- VRYPLTFGWICYKLVPEPDKVEEANKG was predicted by TEPITOPE to bind HLA DR1, DR3, DR4, DR7, DR11, DR15, DRB5.

**HXB2 Location** Nef (136–155)

**Author Location** Nef (136–155 LAI)

**Epitope** PLTFGWCYKLVPEPKVEE

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (151–170)

**Author Location** Nef (151–170 LAI)

**Epitope** DKVEEANKGENTSLHPVSL

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (162–178)

**Author Location** Nef (162–178 B Consensus)

**Epitope** NSLLHPMSLHGMDDEPK

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 11% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** Nef (164–183)

**Author Location** Nef (166–185 HXB3)

**Epitope** LLHPVSLHGMDPEREVLW?

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade HXB3

*HIV component:* Nef

**Species (MHC)** mouse (H-2<sup>b</sup>)

**References** Sandberg *et al.* 2000

- A strong T helper proliferative response against a rec Nef protein was observed 2 weeks after immunization of HLA-A201 transgenic mice in a C57Bl/6 background – the response was weak by 4 weeks post immunization.
- Mice were immunized with nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by a gene gun.
- Primary responses were directed at peptides 106-125, 166-185, and 181-205, indicating a response to multiple epitopes.

**HXB2 Location** Nef (166–185)

**Author Location** Nef (166–185 LAI)

**Epitope** HPVSLHGMDPEREVLWRF

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>b</sup>, H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (176–193)

**Author Location** Nef (176–193 B consensus)

**Epitope** PEKEVLVWKFDSRLAFHH

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0101, DRB1\*0401, DRB1\*0701, DRB1\*1101, DRB1\*1302, DRB1\*1501, DRB5\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 36% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.

- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 7/8 tested HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** Nef (179–198)

**Author Location** Nef (181–205 HXB3)

**Epitope** EVLEWRFDLSRLAFHHVAREL?

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade HXB3

*HIV component:* Nef

**Species (MHC)** mouse (H-2<sup>b</sup>)

**References** Sandberg *et al.* 2000

- A strong T helper proliferative response against a rec Nef protein was observed 2 weeks after immunization of HLA-A201 transgenic mice in a C57Bl/6 background – the response was weak by 4 weeks post immunization.
- Mice were immunized with nef DNA under the control of a CMV promotor, coated on gold particles delivered to abdominal skin by a gene gun.
- Primary responses were directed at peptides 106-125, 166-185, and 181-205, indicating a response to multiple epitopes.

**HXB2 Location** Nef (180–194)

**Author Location** Nef (180–194 clade B consensus)

**Epitope** VLEWRFDLSRLAFHHV

**Subtype** B

**Immunogen** HIV-1 infection, computer prediction

**Species (MHC)** human (DRB1\*0101, DRB1\*0701, DRB1\*1101, DRB1\*1501, DRB5\*0101)

**Country** Brazil

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , HLA binding

**Keywords** binding affinity, computational epitope prediction, cross-presentation by different HLA

**References** Fonseca *et al.* 2006

- TEPITOPE algorithm was used to screen the most conserved regions of clade B consensus sequence for multiple HLA-DR binding epitopes. Peptides predicted to bind 16 or more HLA-DR molecules were synthesized and further assessed in binding assays and for T-cell recognition in a cohort of 32 Brazilian HIV-1 chronically infected individuals.
- While VLEWRFDLSRLAFHHV is the reacting peptide, shorter WRFDLSRLAF peptide was predicted by TEPITOPE to bind HLA-DR molecules. Flanking amino acids were added to increase the efficiency of *in vitro* peptide presentation to CD4 T cells.

**HXB2 Location** Nef (180–202)

**Author Location** Nef (180–202)

**Epitope** VLEWRFDLSRLAFHHVARELHPEY

**Epitope name** Nef-1

**Immunogen** HIV-1 infection

**Species (MHC)** human (DR)

**Country** France

**Assay type** proliferation

**Keywords** computational epitope prediction, cross-presentation by different HLA

**References** Pancré *et al.* 2007

- Responses to 4 Nef epitopes (3 HLA-DR epitopes selected with TEPITOPE software and 1 HLA-DQ epitope) were evaluated in treatment naive asymptomatic patients and long term non-progressors. 2 years later, more than half medium- and non-responders followed bi-therapy, while high responders to Nef peptides still were without antiretroviral treatment and conserved stable CD4 counts, indicating that Nef specific CD4+ response is associated with non-progression.
- Proliferative response to Nef epitopes was always associated with high IFN- $\gamma$  secretion.
- VLEWRFDLSRLAFHHVARELHPEY was predicted by TEPITOPE to bind HLA DR1, DR3, DR4, DR7, DR11, DR15, DRB5.

**HXB2 Location** Nef (181–188)

**Author Location** Nef (185–192 SF2)

**Epitope** LVWRFDLSK

**Epitope name** 6.38

**Subtype** B

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (DP5)

**Donor MHC** DP5, DQw7, DRw11, DRw52

**Assay type** proliferation

**Keywords** epitope processing

**References** Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.

**HXB2 Location** Nef (181–205)

**Author Location** Nef (181–205 LAI)

**Epitope** LEWRFDLSRLAFHHVARELHPEYFKN

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade LAI

*HIV component:* Nef, Rev, Tat

**Species (MHC)** mouse (H-2<sup>d</sup>)

**References** Hinkula *et al.* 1997

- Stronger, broader responses were observed in animals vaccinated with DNA epidermally rather than with intramuscular protein.
- Some proliferative response to vaccination was observed to peptides throughout Nef and Tat, less for Rev.

**HXB2 Location** Nef (182–205)

**Author Location** Nef (182–205 LAI)

**Epitope** EWRFDLSRLAFHHVARELHPEYFKN

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* lipopeptide

**Species (MHC)** human

**References** Gahery-Segard *et al.* 2000

- Anti-HIV lipopeptide vaccine consisting of six long peptides derived from Nef, Gag and Env HIV-1 proteins modified by a palmitoyl chain was administered in a phase I trial.
- A CD4+ T cell proliferative response to at least one of the six peptides was observed in 9/10 vaccinees – 4/10 reacted to this Nef peptide.
- 9/12 tested mounted a CTL responses to at least one of the six peptides, each of the six peptides elicited a CTL response in at least one individual.
- None of the 12 tested had an IgG response to this peptide.

**HXB2 Location** Nef (184–199)

**Author Location** Nef (184–199 B consensus)

**Epitope** KFDSRLAFHHMARELH

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human (DRB1\*0101, DRB1\*0701, DRB1\*1101, DRB1\*1501, DRB5\*0101)

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$

**Keywords** supervised treatment interruptions (STI), immunodominance

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 25% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The peptides that were recognized by the most people were able to bind broadly to multiple HLA-DR molecules. This peptide showed high cross-reactive binding capacity and bound to 5/8 tested HLA-DR molecules.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** Nef (184–199)

**Author Location** Nef (184–199)

**Epitope** KFDSRLAFHHMARELH

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Netherlands

**Assay type** Cytokine production

**References** Geels *et al.* 2006

- The relationship between CTL escape and the subsequent increase in viral load and CD4 Th responses was studied in 2 patients. In both patients T-cell reactivity and recognition were lost after CTL escape, and in 1 patient only the loss of CTL responses was paralleled by a decrease in IL-2 CD4 Th responses.

- Autologous sequences corresponding to known and predicted Th epitopes were analyzed. KFDSRLAFHHMARELH had fixation of 2 mutations (KFDS[r/h]LAF[h/r]HMARELH) in 1 of the patients.

**HXB2 Location** Nef (185–200)

**Author Location** Nef (183–198)

**Epitope** FDSRLAFHHVARELHP

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** Ranki *et al.* 1997

- T-cell response to this epitope persisted after seroreversion.

**HXB2 Location** Nef (186–206)

**Author Location** Nef (p27) (185–205 BRU)

**Epitope** DSRLAFHHVARELHPEYFKNC

**Epitope name** PF63

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BRU

*HIV component:* gp160, Nef, p17/p24 Gag,

p25 Gag *Adjuvant:* muramyl-dipeptide

base adjuvant (Syntex)

**Species (MHC)** chimpanzee

**Keywords** immunodominance

**References** Bahraoui *et al.* 1990

- Six chimpanzees were immunized with rec vaccinia viruses (VV) expressing HIV-1 gp160, Gag, and Nef.
- 2/6 chimpanzees showed persistent T-helper proliferative responses against a putative immunodominant epitope located at the C-term end of Nef.

**HXB2 Location** Nef (189–203)

**Author Location**

**Epitope** LAFHHVARELHPEYF

**Epitope name** N048

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Country** Canada

**Assay type** proliferation, Flow cytometric T-cell cytokine assay

**Keywords** memory cells

**References** Younes *et al.* 2003

- HIV-1-specific CD4+ T-cell responses were analyzed for 6 years since primary infection, in 10 aviremic and 8 viremic patients.
- CD4+ T cells proliferating responses were correlated with the frequency of CD4+ T cells secreting IL-2 in aviremic patients. In viremic patients, CD4+ T cell proliferative response was impaired despite of the high frequencies of IFN- $\gamma$ , but not IL-2-producing CD4+ T cells in periods of elevated viremia, suggesting that long-term CD4+ memory depends on IL-2-producing CD4+ T cells and that IFN- $\gamma$  only-producing cells are short lived.

**HXB2 Location** Nef (190–206)

**Author Location** Nef (190–206 B Consensus)

**Epitope** AFHHMARELHPEYKDC

**Subtype** B

**Immunogen** HIV-1 infection



**Species (MHC)** human

**Country** United States

**Assay type** CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining, HLA binding

**Keywords** supervised treatment interruptions (STI), rate of progression, immunodominance, acute/early infection

**References** Kaufmann *et al.* 2004

- CD4 T-cell responses in 36 HIV-1 positive individuals in different disease stages were mapped by IFN- $\gamma$  EliSpot using a panel of 410 B-consensus peptides spanning all HIV proteins. Virus specific CD4+ T-cell responses (median=7, range of magnitude=990) were detected in 30/36 patients.
- This peptide was recognized by 14% of the study group.
- Gag and Nef responses dominated the CD4+ T-cell EliSpot responses in the study. No correlation between plasma viremia and the frequency or magnitude of HIV-1-specific responses was observed.
- The most HIV-1 specific CD4+ T-cell responses were observed in acutely infected patients with treatment of primary infection who stopped after 1-3 treatments (acute STI), compared to patients continuing therapy. People with therapy during chronic infection had low responses; higher numbers of responses were seen among untreated people. 2/9 LTNPs responded to many peptides, comparable to acute STI.

**HXB2 Location** Nef (191–199)

**Author Location** Nef (195–203 SF2)

**Epitope** FHHMARELH

**Epitope name** 3.2

**Subtype** B

**Immunogen** *in vitro* stimulation or selection

**Species (MHC)** human (DR1)

**Donor MHC** DP4, DQw1, DQw7, DR1, DR8, DRw52

**Assay type** proliferation

**Keywords** epitope processing

**References** Wentworth & Steimer 1994

- Seven CD4+ T-cell clones that proliferated in responses to SF2 Nef were generated *in vitro* by stimulation of PBMC from uninfected donors. These CD4+ clones also had cytotoxic activity.
- These seven clones were capable as of presenting their epitopes to themselves, if Nef peptides were provided.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Nef, Vif, Vpu

**Species (MHC)** mouse (H-2<sup>d</sup>)

**Keywords** subtype comparisons, Th1

**References** Ayyavoo *et al.* 2000

- Splenocytes from BALB/c mice immunized with pVVN-P DNA were incubated with Vif, Vpu or Nef antigens for 3 days and assayed for IL-4 and IFN- $\gamma$  levels.
- Antigen stimulation increased IFN- $\gamma$  production in pVVN-P immunized mice, indicating a Th1 response.
- IL-4 production was not significantly changed after antigen stimulation compared to control levels.

- Cross-clade CTL activity was also observed: A, B clade, CRF01(AE) clade antigens could serve as targets for the B clade immunization stimulated CTL – an HIV-1 AC recombinant, however, did not stimulate a CTL response, but was expressed at lower levels on the target cell.

**HXB2 Location** Nef

**Author Location** Nef (LAI)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**References** da Silva & Hughes 1998

- This study compares the level of variation in Nef CTL epitopes to helper and MAb epitopes from the same region.
- CTL epitopes tend to be more conserved than either helper or MAb epitopes and there are stronger functional constraints in the regions where CTL epitopes cluster.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Nef, Rev, Tat

**Species (MHC)** human

**Keywords** HAART, ART

**References** Calarota *et al.* 1999

- 9/9 HIV-1 + subjects were given one of three DNA vaccinations for nef, rev or tat, and novel proliferative and CTL responses were generated.
- The nef DNA immunization induced the highest and most consistent CTLp activity, IFN- $\gamma$  production, and IL-6 and IgG responses.
- Highly active antiretroviral treatment (HAART) did not induce new HIV-specific CTL responses but reduced viral load, while DNA vaccination induced new immune responses but did not reduce viral load – thus this is a potentially complementary and promising combination.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA *HIV component:* Nef, Rev, Tat *Adjuvant:* CpG immunostimulatory sequence (ISS)

**Species (MHC)** human

**Keywords** review, Th1

**References** Calarota & Wahren 2001

- This review discusses the cellular immune response, and comments on CpG induction of Th1 cytokines and enhanced immune responses, and HIV-1 DNA vaccine boosting of CTL and Th proliferative responses in asymptomatic HIV+ individuals.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** HAART, ART

**References** Oxenius *et al.* 2000

- Patients who started therapy at acute HIV infection (three with sustained therapy, two with limited therapy upon early infection) had strong HIV specific CD4 proliferative responses and were able to maintain a CTL response even with undetectable viral load – three patients that had delayed initiation of HAART had no HIV specific CD4 proliferative responses and lost their CTL responses when HAART was eventually given and their viral loads became undetectable.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** rate of progression, Th1, Th2

**References** Wilson *et al.* 2000b

- Dysfunction of HIV-1 specific proliferative responses, but not responses to other antigens, is evident in HIV-1 progressive disease.
- Vigorous HIV-1 specific responses to p24, Nef and gp120 with SI between 8-99 were seen in 6/7 long term non-progressors (LTNP), the seventh had a borderline responses. IL-2 production was seen in all cases, and IL-4 production was also evident many responses.
- None of the progressors (0/5) had HIV-1 specific proliferative responses, or IL-2 or IL-4 induction.
- Non-HIV antigens (cytomegalovirus, PPD, Staphylococcus enterotoxin B, tetanus toxoid) gave similar responses in HIV-1 + LTNP, progressors, and HIV-1 controls.

**HXB2 Location** Nef

**Author Location** Nef (BRU)

**Epitope**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA), PLG

**Species (MHC)** mouse

**Keywords** Th2

**References** Moureau *et al.* 2002

- BALB/c mice were immunized with Nef alone, Nef with Freund's adjuvant, or Nef encapsulated in poly(DL-lactide-co-glycolide) PLG microparticles.
- High Ab titers (predominantly IgG1) against Nef were retained for seven months in the mice infected with Nef-PLG, 3-fold higher than Nef in Freund's, 5-fold higher than Nef alone.
- CD4+ T-cell lymphoproliferative were observed, and cytokine profiles indicated this was primarily a Th2 response.

**HXB2 Location** Nef

**Author Location** Nef (SF2)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** subtype comparisons, rate of progression

**References** Imami *et al.* 2002b

- 70 patients with chronic disease progression, 10 clinical non-progressors, and 3 immunologically discordant progressors (individuals who controlled viremia but had progressive CD4+ T-cell decline) were analyzed for their T-helper cell responses to p24 and cytokine profile.
- In a comparison of responses to HIV-1 proteins based on 10 non-progressors, 3 immunologically discordant, and 70 progressors, SIs were always much higher for non-progressors and immunologically discordant than progressors. Among the non-progressors, the responses to different antigens were greater using p24 peptides than native p24. Native p24, Nef, gp120 proteins, and Remune (gp120 depleted HIV-1, p24 is subtype G), had roughly comparable distributions of SI values from the non-progressors, Nef and gp120 responses were somewhat diminished in immunologically discordant patients.

**HXB2 Location** Nef

**Author Location** (BRU)

**Epitope**

**Subtype** B

**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* B clade BRU  
*HIV component:* RT, virus  
*Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (MHC)** mouse

**References** Haas *et al.* 1991

- Of 5 mouse inbred lines tested: DBA/2 (H-2d, Ad, Ed), B10.A(4R) (H-2h4, Ak) and B10.A(5R) (H-2i5) showed particularly good CD4+ T cell proliferative responses to HIV proteins (gp160, gp120, p17, p24, Nef and RT), after vaccination with inactivated virus.
- B10.BR (H-2k, Ak, Ek) and C57BL/6 (H-2b and Ab) had weaker responses.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen**

**Species (MHC)**

**References**

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)**

**Assay type** proliferation

**Keywords** HAART, ART

**References** Sullivan *et al.* 2003

- Lymphoproliferative responses to HIV antigens p24, gp120 and Nef were enhanced in eight patients who were switched from protease inhibitors to non-nucleoside reverse transcriptase inhibitors.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** Cytokine production, proliferation

**Keywords** HAART, ART

**References** Hardy *et al.* 2003

- Upon initiating HAART, CD4+ T cell proliferative responses in 36 patients were restored to specific antigens, mitogens, and IL-2. Restored recall responses were largely to persistent antigens, and not to HIV-1 or new antigens, and recall responses were associated with IL-2, not IL-4 production.

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection, in vitro stimulation or selection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** immunotherapy

**References** Kavanagh *et al.* 2006

- Transfection of antigen-presenting cells with a clade B consensus nef construct bearing lysosomal targeting signals produced rapid and prolonged antigen presentation to CD4+ and CD8+ T cells. Lysosome-targeted antigen drove a significantly greater expansion of Nef-specific CD4+ T cells, compared with cytoplasm-targeted antigen.

### III-B-19 HIV-1 Helper/CD4+ T-cell epitopes

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** review, HIV exposed persistently seronegative (HEPS), mother-to-infant transmission

**References** Kuhn *et al.* 2002

- Intrauterine exposure of infants to HIV from their mothers results in HIV-1 specific T-helper cell proliferative responses in 1/3 of exposed uninfected babies, and HIV-1 specific CTL in some. It is unknown whether these responses are associated with lack of infection, but there is some evidence that HIV-1 T-cell responses may reduce transmission in breastfeeding mothers. Summary tables are provided of CD4 and CD8 T-cell responses detected in earlier studies.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human

**Keywords** HAART, ART, rate of progression

**References** Kahn *et al.* 2000

- No benefit was observed in terms of progression free survival for HIV-1 patients on ART given vaccinations with HIV-1 antigen (N=1,262) versus those vaccinated with placebo (N=1,265). There was no statistically different outcome in HIV RNA, CD4 percentage, or body weight. HIV-1 ART patients that were vaccinated did have higher absolute CD4 counts.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human

**Keywords** HAART, ART

**References** Moss *et al.* 1999

- 15 HIV-1 + patients on ARV given vaccinations with HIV-1 antigen versus vaccinated with placebo. Lymphocyte proliferation of CD4+, CD8+ memory cells and NK cells to p24 and Remune HIV-1 antigen increased in HAART treated patients after vaccination.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human

**Keywords** Th1

**References** Moss *et al.* 1997

- HIV-1 specific stimulation of T-cell proliferation, and beta-chemokines (RANTES) and Th1-type cytokine (IFN $\gamma$ ) production are found after immunization of HIV-1 + individuals with HIV-1 immunogen.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *HIV component:* gp120 depleted virus *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human

**References** Levine *et al.* 1996

- Long-term follow up of HIV-1 + individuals given HIV-1 immunogen, suggesting those patients who became HIV-DTH-responsive in response to the HIV-1 immunogen had a better clinical outcome. Of twelve who developed DTH-responsiveness, one got an opportunistic infection and died, and one developed KS. Of the 13 patients who remained HIV-DTH-nonresponsive, 9 (69%) progressed to AIDS and 7 of these had died.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine

*Vector/Type:* HIV-1 immunogen *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (MHC)** human**References** Turner *et al.* 1994

- A dose response study of HIV immunogen in IFA was conducted. Doses of 50, 100, 200, or 400 micrograms (total protein) were tested by DTH skin testing to the inactivated HIV-1 antigen. The HIV-1 immunogen was well tolerated, and the minimum dose required to induce HIV-1 DTH was 100 micrograms.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human, macaque**Keywords** dynamics, HAART, ART**References** Wodarz 2002

- Mathematical modeling is used to support the idea that T-helper cell dysfunction results in a compromised ability to maintain an anti-HIV CTL memory response. Models suggest strategies to restore CTL memory through therapy and improve long-term immunological control of the virus.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection, vaccine

*Vector/Type:* DNA, canarypox, gp120 depleted virus HZ321 (REMUNE(TM)), protein, virus-like particle (VLP), adenovirus *Adjuvant:* GM-CSF, Growth Hormone, IL-12, IL-2, IL-7, CpG immunostimulatory sequence (ISS), Thymosin  $\alpha$ -1

**Species (MHC)** human**Keywords** HAART, ART, review, rate of progression, immunotherapy**References** Imami *et al.* 2002a

- This review addresses the use of immunotherapy and therapeutic immunization to help chronically infected patients maintain a strong anti-HIV-1 T-cell response. The loss of anti-HIV-1 proliferative responses early after infection is reviewed, as are therapeutic vaccinations, with or without HAART, and strategies for immunomodulation that can be given with or without vaccination.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** review, rate of progression, Th1, Th2**References** Heeney 2002

- Review of the importance of balanced Th1 and Th2 HIV-specific CD4 T-cell responses in control of infection and for vaccination strategies.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)****Keywords** dynamics, rate of progression, escape**References** Bernaschi & Castiglione 2002

- A cellular automata model was used to model the dynamics of HIV-1 infection and progression to disease. The model suggests the long asymptomatic period is due to immune escape mutants with lower viral fitness, and with AIDS resulting from a drastic reduction of the T-helper cell reservoir.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine**Species (MHC)****Keywords** dynamics, kinetics**References** Altes *et al.* 2002

- This study employs a mathematical model to study the consequences of increasing the T-helper response through a vaccine, which would have counter-balancing effects in a new infection: a more intense response provides more help but also more target cells. The model indicates that if the infecting virus had a low replication rate, then CTLp and CD4 helper cells could control an infection. Only a vaccine that could increase CTL responsiveness could reduce viral set point with observed replication rates.
- A CD4+ T-cell response without maintained CTL response was deleterious in this model.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)****Keywords** dynamics, HAART, ART, rate of progression**References** Bajaria *et al.* 2002

- This paper presents a dynamical model of HIV infection and progression that includes CD4 T-cell naive and memory populations distributed between the peripheral blood and the lymph nodes, as well as the effects of HAART. Increasing viral replication and infectivity and decreasing T-cell immunity had impact on the rate of disease progression in this model.

**HXB2 Location** HIV-1**Author Location** (HZ321)**Epitope****Subtype** AG

**Immunogen** vaccine

*Vector/Type:* gp120 depleted virus HZ321 (REMUNE(TM)) *Strain:* AG recombinant HZ321 *Adjuvant:* Incomplete Freund's Adjuvant (IFA), CpG immunostimulatory sequence (ISS)

**Species (MHC)** mouse**Keywords** Th1, Th2**References** Ayash-Rashkovsky *et al.* 2002

- Parasitic helminthic infections in humans, common in parts of Africa and Asia, can shift immune responses to Th2 responses. To model this, BALB/c mice were infected with the parasite *Schistosoma mansoni*, and the infected mice showed a dominant Th2 immune response. Vaccination with gp120-depleted HIV-1 viral particles and incomplete Freund's adjuvant induced Th2 responses in these mice, but this could be shifted towards a Th1 profile when CpG oligodeoxynucleotide was added to the vaccine as an immunostimulatory agent.

**HXB2 Location** HIV-1**Author Location** HIV-1 except gp120**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, rate of progression**References** Ghanekar *et al.* 2001

- 12 long term non-progressors (>10 years) went on HAART, while 14 elected not to go on HAART. After a year on HAART, higher frequencies and absolute numbers of HIV-specific memory CD4+ T-cells were observed in untreated patients than patients receiving HAART therapy, tested by stimulation a proliferation responses to HIV Remune antigen (gp120 depleted vaccine).
- These results indicate a control of viral replication in therapy-naive patients may be mediated by their ability to respond to recall viral antigen, and that the diminished response in treated patients may contribute to viral rebound.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** HAART, ART, Th2**References** Pido-Lopez *et al.* 2002

- The thymic output in HAART-treated HIV-1 infected patients with progressive disease was studied. One patient also receiving steroid treatment therapy had a weak response in a sjTREC assay indicating a dysfunctional thymus, while four patients not on steroids had clear positive sjTREC readings after HAART. Stimulation of PBMC with multiple recall antigens including gp120, p24 and Nef and mitogens, and revealed that in the patient treated with steroids there was and induction of a Th2 type response indicated by increased levels of IL-4 secretion in response to antigen.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine

*Vector/Type:* peptide *Adjuvant:* GM-CSF, IL-12, IL-2, IL-4, Tumor Necrosis Factor  $\alpha$  (TNF $\alpha$ )

**Species (MHC)****Assay type** Th support of CTL response**Keywords** binding affinity, review, Th1, Th2, mucosal immunity**References** Berzofsky 2001

- Vaccine clusters were constructed containing T helper, CTL and neutralizing antibody epitopes, and used to immunize mice. Four things were found to enhance the vaccine immune response: i) increasing the affinity of the peptide for the presenting MHC molecule, called epitope enhancement; ii) increasing the avidity of MHC/peptide complex for the T-cell receptor; iii) incorporating cytokines IL-2, GM-CSF, TNF- $\alpha$ , or IL-12 and IL-4 which steer responses towards Th1 or Th2 responses; iv) inducing mucosal immunity specifically, with intrarectal being most effective.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Env, Gag *Adjuvant:* B7, GM-CSF, IL-12, IL-15

**Species (MHC)** human**Keywords** review, Th1, Th2**References** Boyer *et al.* 2002

- The first generation of HIV-1 plasmid vaccines in 167 individuals induced T-helper responses in most vaccine recipients, however CTL responses were below a 20% response rate. REV-independent RNA optimized constructs (pGag and pEnv) as well as B7 costimulatory molecules could significantly enhance CD8 effector cell responses. Co-administered GM-CSF enhanced antibody responses, IL-12 CTL production. IL-15 increased T cell expansion without increasing T cell help.

**HXB2 Location** HIV-1**Author Location** HIV-1**Epitope****Immunogen** HIV-1 infection**Species (MHC)****Assay type** Cytokine production**Keywords** review**References** Breen 2002

- HIV-1 triggers immunological dysfunction in multiple ways, including the loss of CD4-positive T helper cells in quantity and function and hyperactivity and changes in the production and activity of cytokines. The role of pro- and anti-inflammatory cytokines are discussed, including IL-10, which can suppress HIV-1, and IL-1, IL-6, TNF $\alpha$  which up-regulate HIV-1.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Assay type** Cytokine production, proliferation**References** Clerici *et al.* 1993b

- rCD4-IgG treatment was associated with improved Th cell function measured by IL-2 production in response to alloantigen or PHA, but not to influenza (a recall antigen response), in 9/10 patients. No clinical benefit was evident. rCD40IgG was also shown to block gp120 induced suppression of Th cells *in vitro*. Proposed mechanisms include: inhibiting HIV-cell fusion by blocking the binding of gp120 to CD4, competing with free gp120 for binding to the CD4 receptor and reducing gp120 induced immunosuppression, and gp120-induced direct killing of Th cells.

**HXB2 Location** HIV-1

**Author Location** Nef

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** assay standardization/improvement

**References** Draenert *et al.* 2003

- Six different HIV-1 Nef peptide sets ranging in length from 15-20 amino acids with overlap from 10-11 amino acids derived from either the B clade consensus sequences or the B clade sequence B.AU.AF064676 were used to study the impact of using different peptide design strategies to detect CD4 and CD8 T-cell responses. 20 individuals were tested using the six sets of peptides. 17/20 had CD8 T-cell responses to all peptides sets, and 15 of these 17 had CD4 T-cell responses.

**HXB2 Location** HIV-1

**Author Location** Nef

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** assay standardization/improvement

**References** Draenert *et al.* 2003

- Six different HIV-1 Nef peptide sets ranging in length from 15-20 amino acids with overlap from 10-11 amino acids derived from either the B clade consensus sequences or the B clade sequence B.AU.AF064676 were used to study the impact of using different peptide design strategies to detect CD4 and CD8 T-cell responses. 20 individuals were tested using the six sets of peptides. 17/20 had CD8 T-cell responses to all peptides sets, and 15 of these 17 had CD4 T-cell responses.
- Although there was a trend in detecting more CD8 T cell responses using the shorter 15-mer peptides, longer 20-mers were best for detecting more CD4 T-cell responses, but neither result was statistically significant. Similar results were seen in the 15 to 20 amino acid range for both IFN gamma Elispot and ICS assays.
- Use of the consensus versus the natural strain identified slightly increased numbers of reactive peptides. Seven reactive peptides were observed with the B consensus peptides but not the B.AU.AF064676 peptides, but on the other hand four reactivities were observed using the B.AU.AF064676 peptides but not the consensus.

- Using an overlap of 10 or 11 amino acids did not make a difference.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)**

**Assay type** Cytokine production

**Keywords** HAART, ART

**References** Galli *et al.* 2003

- HIV-1-infected women who developed Adefose tissue alterations (ATA) while receiving antiretroviral treatment (ART) had a favorable immunological profile with efficient IL-2 production and T-helper function. The authors suggest that ATA may be related to the ART-driven restoration of immune function.
- The most prominent feature of women with ATA that were receiving ART was increased IL-12 production with a lower TNF alpha and IL-10 synthesis.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)**

**Keywords** review

**References** Norris & Rosenberg 2002

- This paper reviews the role of Th cells in controlling HIV-1 infection, and in other viral infections. It describes CD4+ T-cell support of Ab production, CTL responses, as well as antiviral cytokine production and infected-cell killing. HIV+ patients with a low viral load and rare vigorous HIV-specific CD4+ proliferative responses, and the benefit of early treatment in preserving Th HIV-specific responses allowing immune control when therapy is subsequently stopped, are described.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 infection

**Species (MHC)** human

**Keywords** review, rate of progression, acute/early infection

**References** Norris & Rosenberg 2001

- This review goes over the evidence for HIV-1 specific Th and CTL responses being critical for inhibiting viral replication. LTNPs and those treated during acute HIV-1 infection generate specific Th responses, but most chronically infected individuals do not.

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Immunogen** HIV-1 and GBV-C co-infection

**Species (MHC)** human

**Assay type** Cytokine production

**Keywords** HAART, ART, rate of progression, Th1, Th2

**References** Nunnari *et al.* 2003

- HIV-1 positive patients co-infected the GBV-C, the hepatitis G virus, have a longer survival time to AIDs and higher CD4+ T cell counts than patients that were not infected with GBV-C. GBV-C co-infected patients showed an intact Th-1 profile over time, with high serum levels of IL-2 and IL-12, and diminishing Th-2 responses reflected by lower levels of IL-4 and IL-10. The opposite was true for HIV-1 + patients that were not co-infected with GBV-C.
- AIDs progression is slower in patients infected with both HIV-1 and hepatitis G virus. It is unclear whether Th-2 and Th-1 cytokines in co-infected patients show cause or consequence of slower AIDs progression. CD4+ cells may support hepatitis G replication.

**HXB2 Location** HIV-1**Author Location** HIV-1**Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Keywords** dynamics, acute/early infection**References** Korthals Altes *et al.* 2003

- A model of progression was developed that explicitly assumes CD4+ T-cells are both targets of infection and mediators of the immune response. In this model, high viral inoculum with few initial CD4+ T-cells resulted in target-cell-limited infection and high viral load, but with many CD4+ clones and low initial inoculum, infection was controlled by CD4+ clones.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine

*Vector/Type:* DNA *Adjuvant:* GM-CSF, IFN $\gamma$ , IL-12, IL-15, IL-18, IL-1 $\alpha$ , IL-2, IL-2/Ig, MIP-1 $\alpha$ , Tumor Necrosis Factor  $\alpha$  (TNF $\alpha$ ), Tumor Necrosis Factor  $\beta$  (TNF $\beta$ ), M-CSF, G-CSF, IL-8, SDF-1 $\alpha$ , RANTES, MCP1

**Species (MHC)****Keywords** review, Th1, Th2, adjuvant comparison**References** Calarota & Weiner 2004

- Review summarizes the developments of DNA vaccine enhancement/modulation by 1) improving Th1 cytokine-encoding plasmids 2) by prime-boost vaccine regimens and 3) by chemokine- or T-cell costimulatory molecule encoding plasmids. Studies involving many approaches for stimulating Th1 responses upon vaccination are compared, and given the initial promise of these strategies, future studies of coadministration or prime boosting with different combinations are advocated.

**HXB2 Location** HIV-1**Author Location** p24 (HIV-2 ROD, HIV-1 IIIB)**Epitope****Immunogen** HIV-1 or HIV-2 infection**Species (MHC)** human**Country** Gambia**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ , Chromium-release assay**Keywords** rate of progression**References** Jaye *et al.* 2004

- A comparison of T cell responses in HIV-1 and HIV-2 infected asymptomatic patients with CD4+ cell counts of 20% showed no significant difference between both groups. Viral loads were roughly 20 times greater in HIV-1 positive patients than HIV-2 positive patients.
- 10/20 (50%) of HIV-1 infected patients demonstrated proliferative responses with SI greater than 1.4 to gp120, and 11/20 to p24. 8/29 (29%) of HIV-2 infected patients recognized gp105, and 8/29 (29%) p26. Cytokine responses in both groups did not differ.
- 9/21 (43%) of HIV-1 + and 15/30 (50%) of HIV-2 + patients had cytotoxic T cell responses to Gag, and 3/21 (14%) HIV-1 + and 8/30 (27%) HIV-2 + responded to Pol.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Country** Spain**Assay type** proliferation, Intracellular cytokine staining**Keywords** HAART, ART**References** López *et al.* 2004

- A clinical trial compared chronically HIV-1 infected patients who had replaced HAART with didanosine (ddI) and hydroxyurea (HU) were followed for 12 months to an untreated HIV+ group and a group that continued on HAART.
- Approximately 20% of the patients treated with ddI-HU had detectable CD4+ T-cell proliferative responses to Gag and Env in contrast to drug-naive and HAART treated HIV-infected patients, who had few or no responses.
- HIV-specific CD8+ T-cell responses were higher in ddI-HU treated patients than HAART treated patients, even in individuals that maintained undetectable viral loads.

**HXB2 Location** HIV-1**Author Location** Tat (89.6)**Epitope****Immunogen** vaccine

*Vector/Type:* DNA prime with protein boost, ISCOM *Strain:* B clade IIIB, SIV *HIV component:* Env, Gag, Tat *Adjuvant:* Immune stimulating complexes (ISCOM)

**Species (MHC)** macaque**Assay type** Cytokine production, proliferation, CD8 T-cell Elispot - IFN $\gamma$ **Keywords** vaccine-specific epitope characteristics, Th1, Th2, vaccine antigen design**References** Mooij *et al.* 2004

- This study compared vaccinating with Tat alone to vaccinating with Tat+Gag+Env. Rhesus macaques (*Macaca mulatta*) were intramuscularly immunized with a combination of DNA plasmids (HIV-1 IIIB expressing Tat, SHIV-1 89.6P expressing gp120 and SIV mac239 expressing Gag, followed by three boosts with HIV-1 Tat (IIIB) and Env (89.6, gp140) SIV Gag protein. Animals with multi-antigen vaccination had reduced viremia increased CD4+ T-cell counts.

- Tat-Env-Gag immunized animals had weaker Tat-specific Th responses in comparison to animals immunized with Tat alone; but the response to Tat alone was a Th2 response that did not protect from challenge.
- Immunization with Tat-Env-Gag boosted proliferation of Gag-specific IFN- $\gamma$  and IL-2 producing cells in 3/4 animals (Th1 and Th2 responses) and induced a Th2-immune response (IL-2, IL-4) to Env.
- CD4+ T helper responses to Tat-Env-Gag immunization were correlated with control and reduction of viremia, suggesting a combination of Th1 and Th2 vaccine responses to multiple HIV antigens is advantageous.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** vaccine**Species (MHC)** macaque**Keywords** review**References** Heeney 2004

- Review discusses the status, design and selection of novel HIV vaccines which elicit strong T-helper responses which can in turn can elicit CTL and Ab responses.
- Review discusses the status, design and selection of novel HIV vaccines which elicit strong T-helper responses which can in turn can elicit CTL and Ab responses.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection, vaccine**Species (MHC)** human**Keywords** review, immunotherapy, adjuvant comparison**References** Wahren & Liu 2004

- This review covers immunotherapeutic vaccines use in combination with antiretroviral therapy and use of vaccination in combination with adjuvants and immunomodulators.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen****Species (MHC)****Keywords** review, adjuvant comparison**References** Mitchison & Sattentau 2005

- Review summarizes mechanisms of immunoregulation relevant for new vaccine development, with a brief summary of adjuvant triggering innate immunity through Toll-like receptors (TLRs), Nod molecules, and other activators. DNA encoded adjuvants that have been tested in DNA vaccines are summarized. The balance between Th1 (CTL activating) and Th2 (B cell activating) responses is discussed, and it is noted that BALB/c mice are predominately Th2 responders, C57BL Th1.

**HXB2 Location** HIV-1**Author Location****Epitope****Subtype** C**Immunogen** HIV-1 infection**Species (MHC)** human**Country** South Africa**Assay type** Flow cytometric T-cell cytokine assay**References** Ramduth *et al.* 2005

- The magnitude of HIV-specific CD8+ T cell responses in HIV-1 infected individuals from South Africa correlated with the CD4+ T cell responses. CD4 responses were narrowly focused, with Gag as dominant target, while CD8 responses were equally distributed among Gag, Pol and the regulatory and accessory proteins. The preferential targeting of Gag by CD8+ T-cells was associated with enhanced control of viral load.

**HXB2 Location** HIV-1**Author Location****Epitope****Immunogen** HIV-1 infection**Species (MHC)** human**Country** South Africa**Assay type** Intracellular cytokine staining**Keywords** assay standardization/improvement**References** Meddows-Taylor *et al.* 2007

- A whole blood peptide mapping intracellular cytokine staining assay was developed, that allows the direct comparison, at individual peptide level, of CD4+ and CD8+ T cell responses. This assay also allows monitoring of the responding cell type in the same reaction and requires considerably less blood than would be necessary if PBMC were first isolated prior to peptide stimulation.
- 396 overlapping peptides across Gag, Pol, Nef, Env, Tat, Rev, Vif, Vpr, Vpr were tested. CD8+ responses were higher in magnitude and in frequency than CD4+ responses in HIV patients screened by this method.

**HXB2 Location** HIV-1**Author Location** Env (MN)**Epitope****Subtype** B**Immunogen** HIV-1 infection, SHIV infection**Species (MHC)** macaque**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining**Keywords** assay standardization/improvement**References** Chea *et al.* 2005

- The study describes a novel in vivo killing (IVK) assay using overlapping peptide pools pulsed onto autologous fluorescently labeled PBMC. Analysis of SIV/HIV specific immunity in several weeks following JVK assays showed a marked enhancement of virus-specific CD8 and CD4 T-cell immunity.

**HXB2 Location** HIV-1**Author Location** Tat (B clade consensus)**Epitope****Subtype** B**Immunogen** HIV-1 infection, SHIV infection**Species (MHC)** macaque**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining



**Keywords** assay standardization/improvement

**References** Chea *et al.* 2005

- The study describes a novel in vivo killing (IVK) assay using overlapping peptide pools pulsed onto autologous fluorescently labeled PBMC. Analysis of SIV/HIV specific immunity in several weeks following JVK assays showed a marked enhancement of virus-specific CD8 and CD4 T-cell immunity.

**HXB2 Location** HIV-1

**Author Location** Vpu (B clade consensus)

**Epitope**

**Subtype** B

**Immunogen** HIV-1 infection, SHIV infection

**Species (MHC)** macaque

**Assay type** CD8 T-cell Elispot - IFN $\gamma$ , CD4 T-cell Elispot - IFN $\gamma$ , Intracellular cytokine staining

**Keywords** assay standardization/improvement

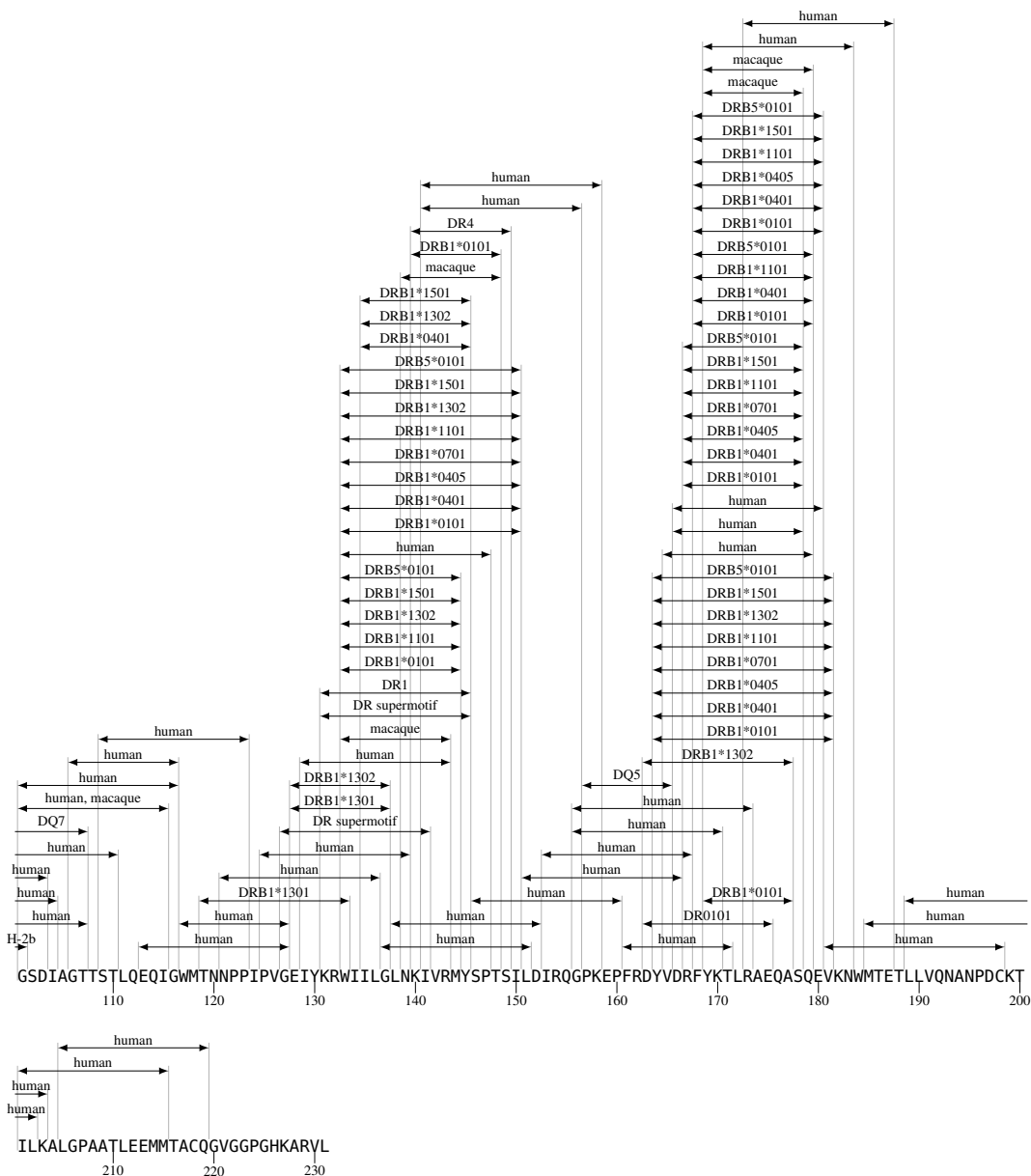
**References** Chea *et al.* 2005

- The study describes a novel in vivo killing (IVK) assay using overlapping peptide pools pulsed onto autologous fluorescently labeled PBMC. Analysis of SIV/HIV specific immunity in several weeks following JVK assays showed a marked enhancement of virus-specific CD8 and CD4 T-cell immunity.

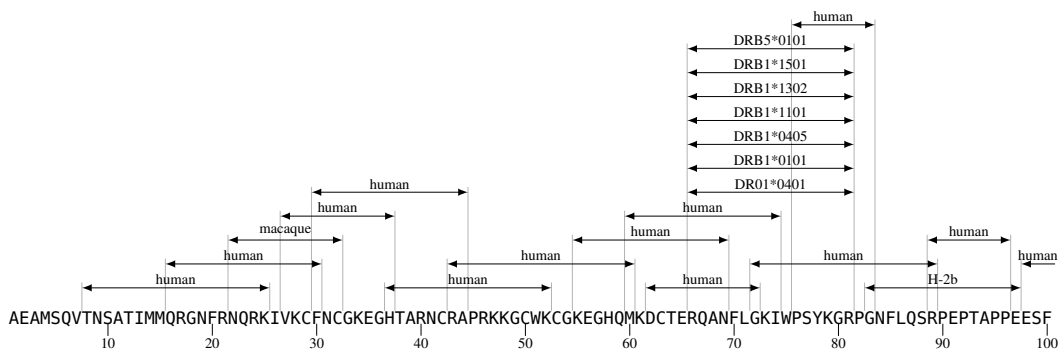


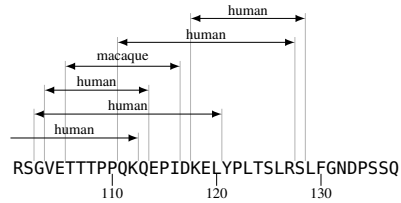


T-Helper CD4 +



III-C-3 p2p7p1p6 T-Helper/CD4 + Epitope Map

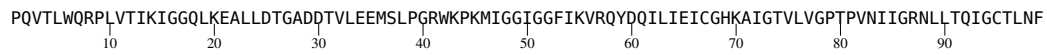




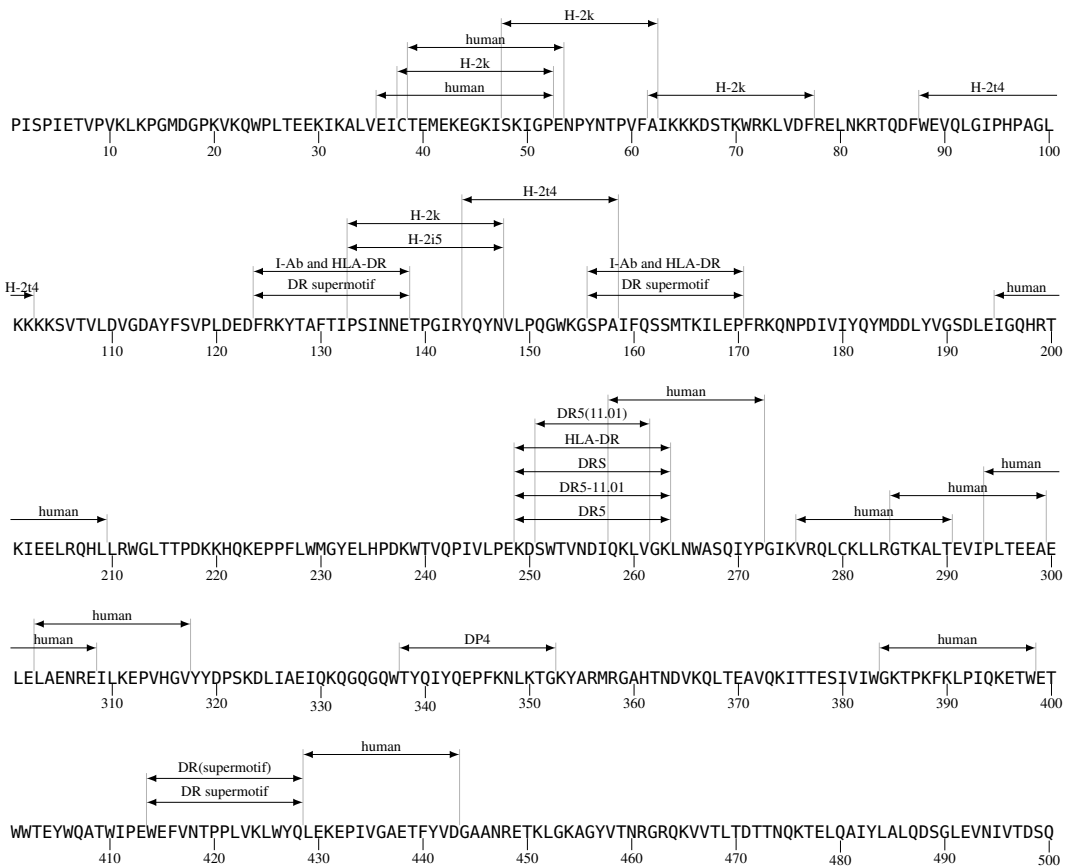
III-C-4 Gag/Pol TF T-Helper/CD4+ Epitope Map



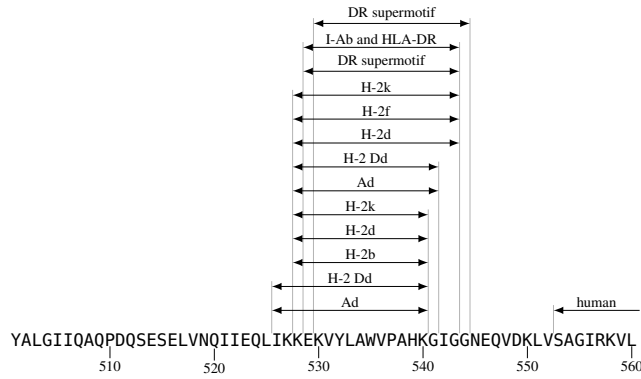
III-C-5 Protease T-Helper/CD4+ Epitope Map



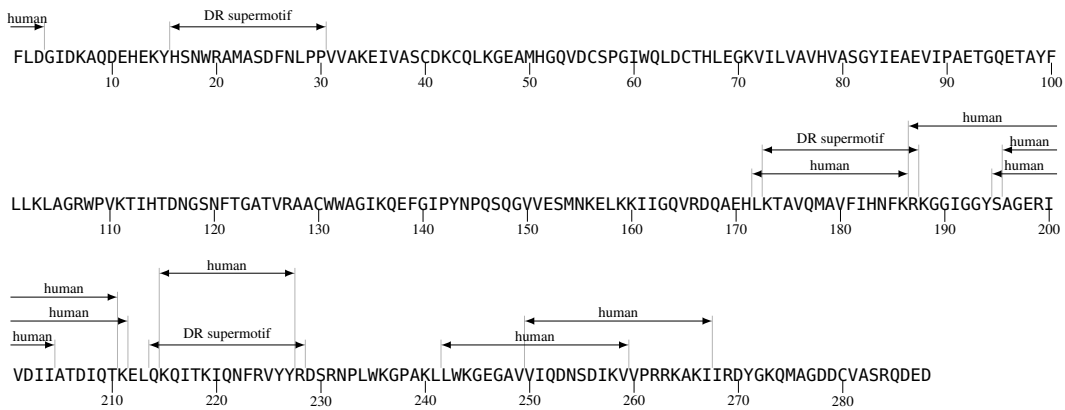
III-C-6 RT T-Helper/CD4+ Epitope Map



T-Helper CD4+

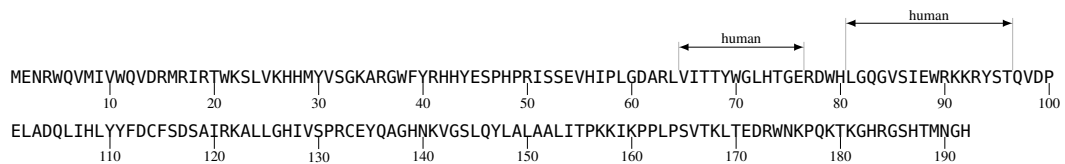


### III-C-7 Integrase T-Helper/CD4+ Epitope Map

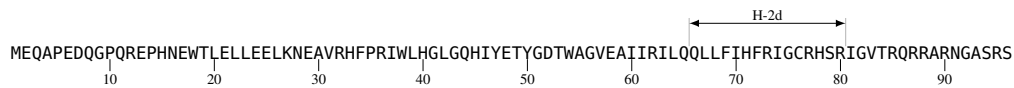


T-Helper CD4 +

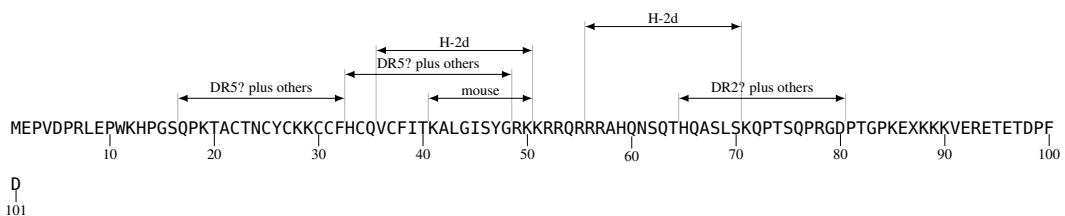
### III-C-8 Vif T-Helper/CD4+ Epitope Map



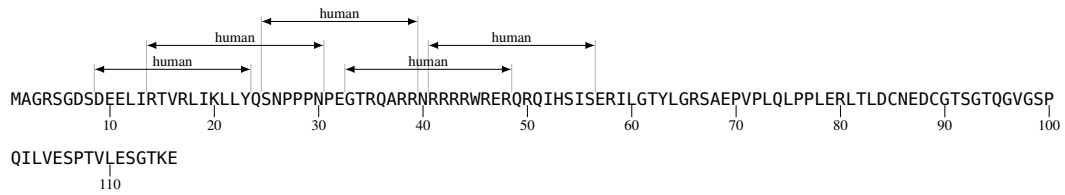
### III-C-9 Vpr T-Helper/CD4+ Epitope Map



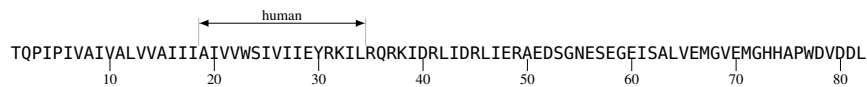
### III-C-10 Tat T-Helper/CD4+ Epitope Map



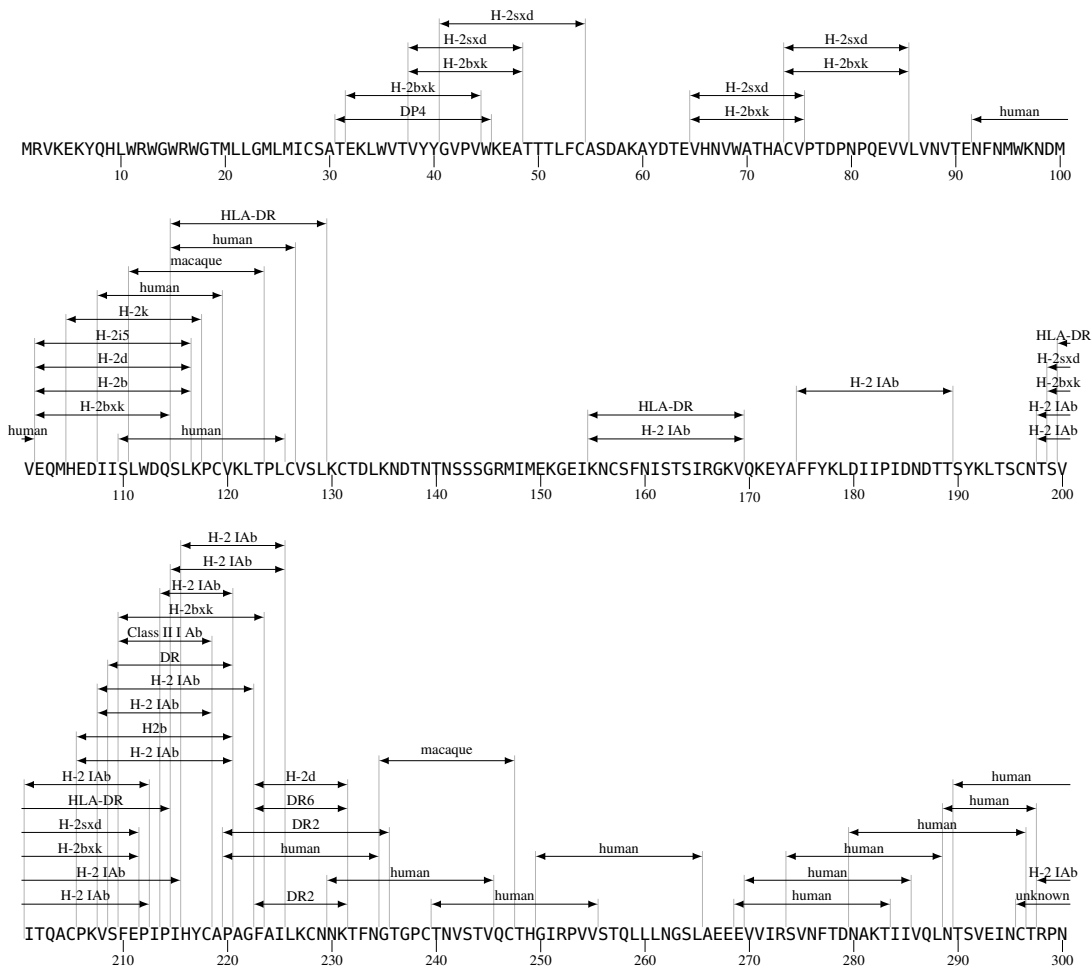
III-C-11 Rev T-Helper/CD4+ Epitope Map



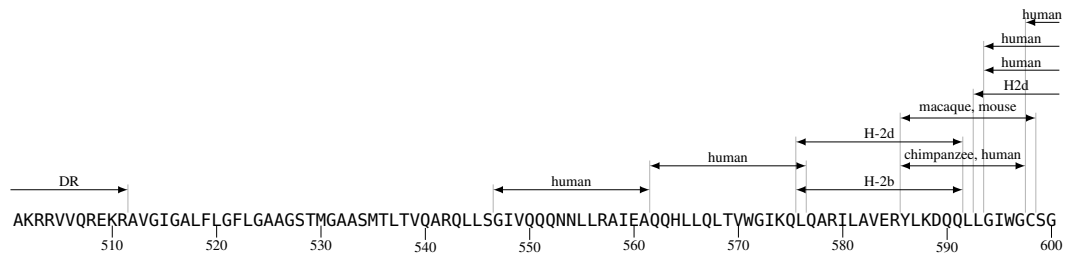
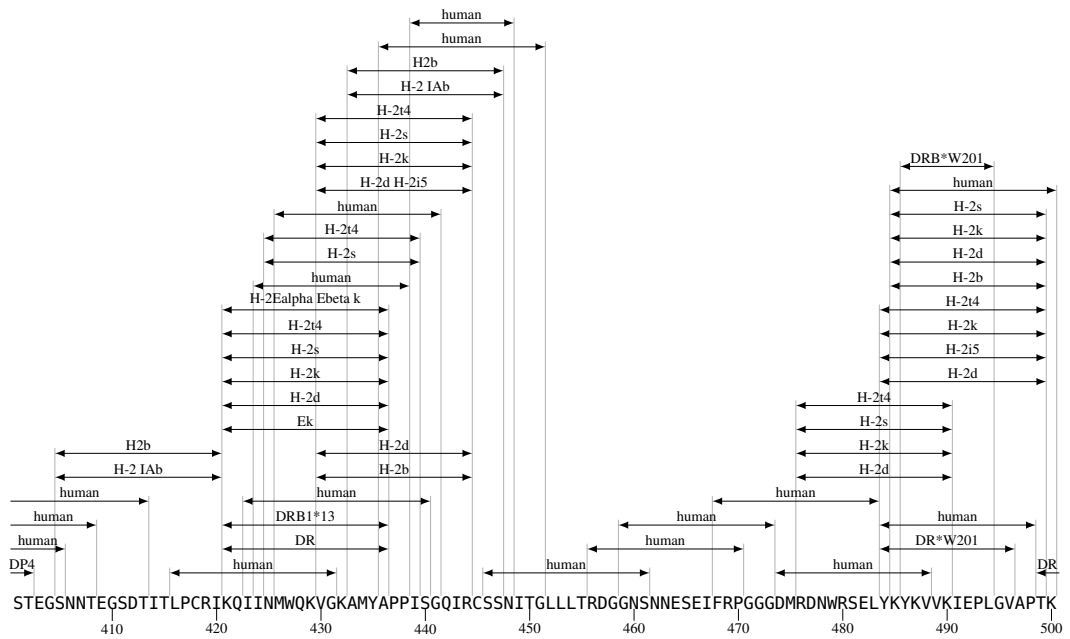
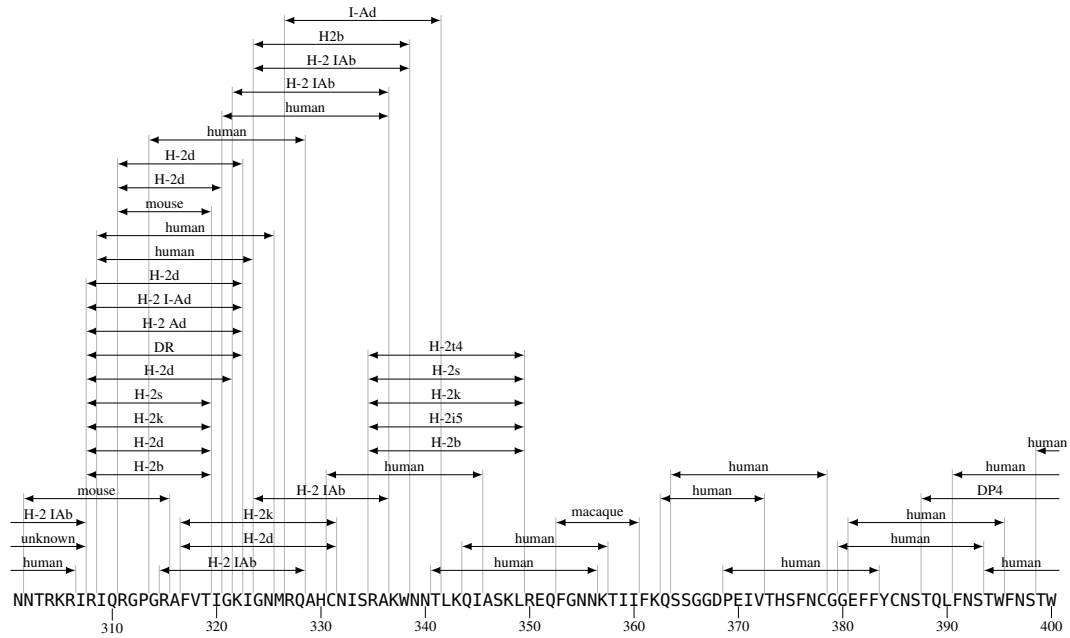
III-C-12 Vpu T-Helper/CD4+ Epitope Map



III-C-13 gp160 T-Helper/CD4+ Epitope Map

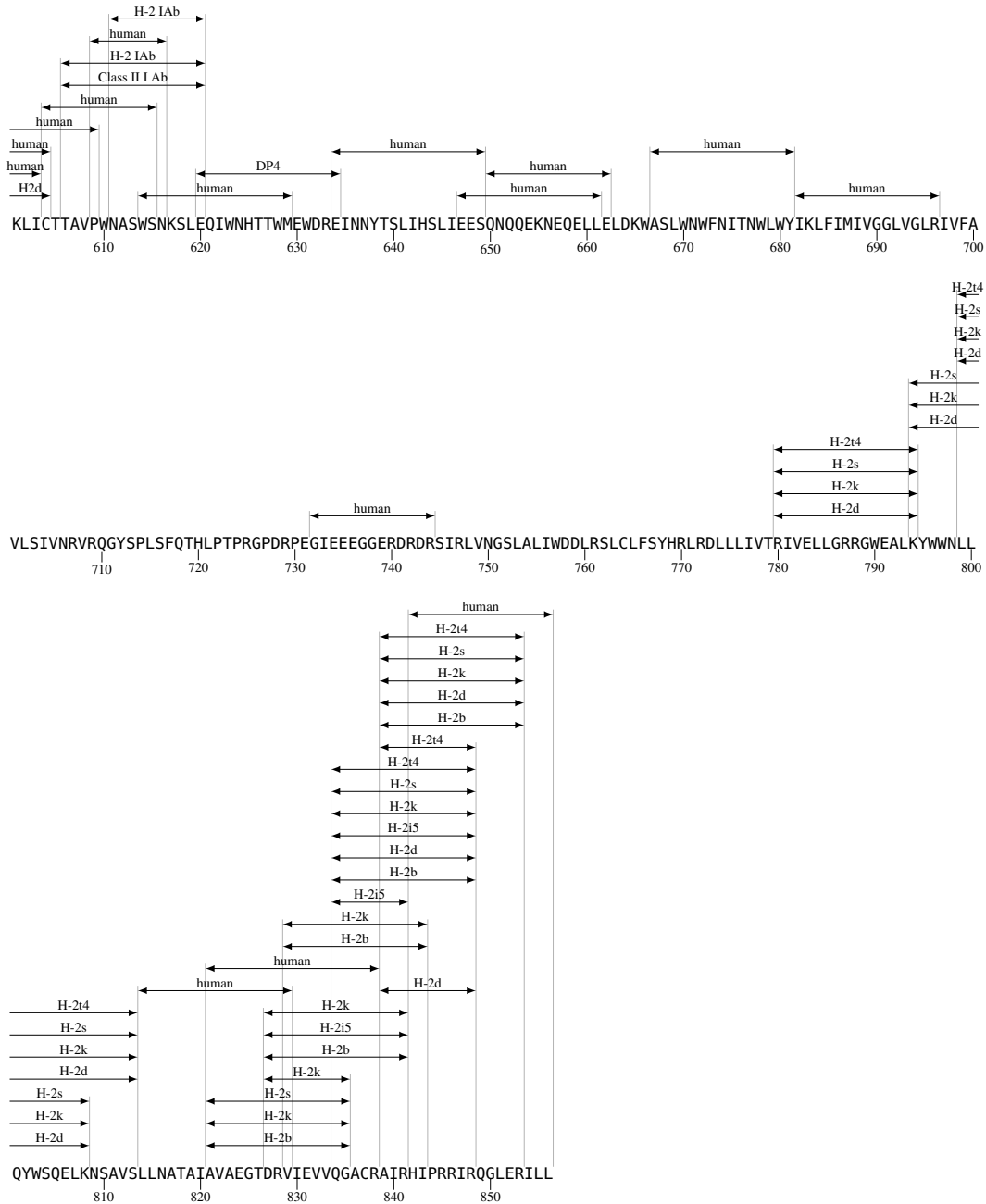


T-Helper CD4+



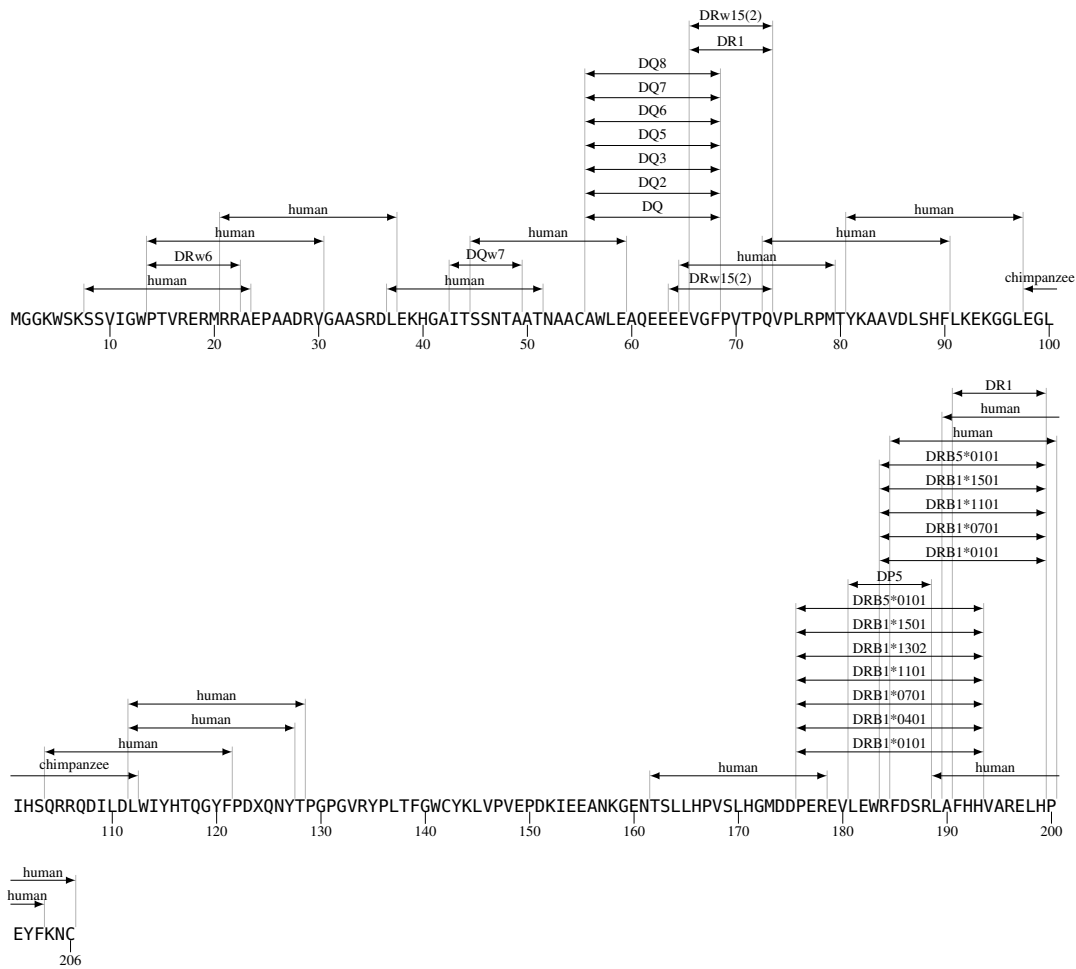
T-Helper CD4 +





T-Helper CD4+

III-C-14 Nef T-Helper/CD4+ Epitope Map



T-Helper CD4 +

**Part IV**

# **HIV Antibody Binding Sites**

**B Cell**



## IV-A

# Summary

This part summarizes HIV-specific antibodies (Abs) from the literature arranged sequentially according to the location of their binding domain, organized by protein. We attempted to make this part as comprehensive as possible. For the monoclonal antibodies (MAbs) capable of binding to linear peptides, we require that the binding site be contained within a region of 30 or so amino acids to define the epitope, but not that the precise boundaries be defined. MAbs that do not bind to defined linear peptides are grouped by category at the end of each protein. Antibody categories, for example CD4 binding site (CD4BS) antibodies, are also noted in the index at the beginning of this part. Studies of polyclonal Ab responses are also included. Responses that are just characterized by binding to a protein, with no known specific binding site, are listed at the end of each protein. For more recent updates, epitope sequence alignments, and search capabilities, please see our web site: <http://www.hiv.lanl.gov/content/immunology>.

### IV-A-1 Indices

Three indices are provided. The first provides a concise list of anti-HIV-1 MAbs by cross-competition category, with both discontinuous epitopes (for example, CD4BS) and some well known linear epitopes (for example, cluster I) summarized. The second lists the MAbs' IDs in alphabetical order so one can find their location in the table. The third is a listing by order of appearance in the tables.

### IV-A-2 Tables

Each MAb has a twelve-part basic entry:

**Number:** Order of appearance in this table.

**MAb ID:** The name of the monoclonal antibody with synonyms in parentheses. MAbs often have several names. For example, punctuation can be lost and names are often shortened (M-70 in one paper can be M70 in another). Polyclonal responses are listed as "polyclonal" in this field.

**HXB2 location:** Position of the antibody binding site relative to the viral strain HXB2 (GenBank Accession Number K03455), which is used as a reference strain throughout this publication. The numbering in this table corresponds to the protein maps. Because of HIV-1 variation, the epitope may not actually be

present in HXB2; rather, the position in HXB2 indicates the position aligned to the epitope. HXB2 was selected as the reference strain because so many studies use HXB2, and because crystal structures for HXB2-related proteins are available. The precise positions of an epitope on the HXB2 reference strain can be readily obtained using the interactive position locator at our web site: <http://www.hiv.lanl.gov/content/sequence/LOCATE/locate.html>.

**Author location:** The amino acid positions of the epitope boundaries and the reference sequence used to define the epitope are listed as given in the primary publication. Frequently, these positions as published are imprecise, and do not truly correspond to the numbering of the sequence, but they provide a reasonable guide to the peptide's approximate location in the protein. Also, in many cases, position numbers were provided but the reference sequence identification was not. Because of HIV-1's variability, position numbers require a reference strain to be meaningful. Binding sites that cannot be defined through peptide binding or interference studies are labeled as discontinuous. The approximate location on the protein, sequence number, and reference sequence are listed.

**Sequence:** The amino acid sequence of the binding region of interest, based on the reference strain used in the study defining the binding site. On occasions when only the position numbers and not the actual peptide sequence were specified in the original publication, we tried to fill in the peptide sequence based on the position numbers and reference strain. If the sequences were numbered inaccurately by the primary authors, or if we made a mistake in this process, we may have misrepresented the binding site's amino acid sequence. Because of this uncertainty, epitopes that were not explicitly written in the primary publication, that we determined by looking up the reference strain and the numbered location, are followed by a question mark in the table.

**Subtype:** The subtype under study, generally not specified for B subtype.

**Neutralizing:** **L:** neutralizes lab strains. **P:** neutralizes at least some primary isolates. **no:** does not neutralize. No information in this field means that neutralization was either not discussed or unresolved in the primary publications referring to the MAb.

**Immunogen:** The antigenic stimulus of the original B cell response. Often this is an HIV-1 infection. If a vaccine was used as the original antigenic stimulation, not a natural infection, this is noted, and additional information about the vaccine antigen is provided as available.

**Species (Isotype):** The host in which the antibody was generated, and the isotype of the antibody.

**Research Contact:** Information about who produced an antibody, how to obtain it, or who should receive credit.

**Country:** The country where the samples were obtained; this is generally not specified if the study was conducted in the United States.

**References:** All publications that we could find that refer to the use of a specific monoclonal antibody. First is a list of all references. Additional details for some of the older references can be found in Part V, although we have tried to keep the entries self-contained since 1997.

**Keywords:** Keywords for antibody entries were initiated in 2004. The keywords are listed when available as part of the main entry, and also follow the note in bold type so references pertaining to particular types of studies can be found quickly.

**Notes:** Describe the context of each study, and what was learned about the antibody in the study.

### IV-A-3 HIV protein binding site maps

The names of MAbs and the location of well characterized linear binding sites of 21 amino acids or less are indicated relative to the protein sequences of the HXB2 clone. This map is meant to provide the relative location of epitopes on a given protein, but the HXB2 sequence may not actually bind to the MAb of interest, as it may vary relative to the sequence for which the epitope was defined. Above each linear binding site, the MAb name is given followed by the species in parentheses. Human is represented by 'h', non-human primate by 'p', mouse by 'm', and others by 'o'. More precise species designations for any given MAb can be found using the web search interface or in the tables in this part.

### IV-A-4 Alignments

To conserve space, no epitope alignments are provided in this book, but they can be generated using the Ab search tool at <http://www.hiv.lanl.gov/content/immunology>. The master alignment files from which the epitope alignments were created are available at our web site at <http://www.hiv.lanl.gov/content/sequence/NEWALIGN/align.html>.

## IV-B

# Cross Reference Listing of MAbs

### IV-B-1 MAbs by binding type

Cross reference by protein and binding type of MAb names and their order of appearance in the tables.

Binding type	MAb ID (No.)
<b>p17</b>	
C-term	sc-FV p17 (35)
<b>p24</b>	
C-term	13B5 (116)
<b>Protease</b>	
N-term	1696 (178)
flap region	F11.2.32 (180)
<b>RT</b>	
gp120 C2	polyclonal (186)
<b>Integrase</b>	
Integrase DNA binding domain	5D9 (218), 2-19 (221), 8-22 (222), 4-20 (223), 6-19 (224)
Integrase catalytic core	7-16 (215), 4F6 (216)
N-term	1C4 (202), 2C11 (203), 2E3 (204), 3E11 (205), 3F9 (206), 5F8 (207), 6G5 (208), 7B6 (209), 7C6 (210), 6C5 (211), 4D6 (214)
<b>Pol</b>	
C-term	33 (254), F-6 (255)
RT palm domain	6B9 (256)
RT thumb domain	5F (257), 5G (258), 7C4 (259)
gp120 V3	polyclonal (253)
<b>Vif</b>	
C-term	TG001 (261)
<b>Tat</b>	
C-term	polyclonal (265), polyclonal (277), polyclonal (278), 1D2F11 (280), 2D9E7 (281), 4B4C4 (282), 5G7D8 (283), NT2/4D5.24 (286), polyclonal (287), 2D9D5 (297), polyclonal (298), polyclonal (299), polyclonal (300)
N-term	polyclonal (265), TA9 (267), TD84 (268), TE135 (269), polyclonal (270), NT3/2D1.1 (271), 1D9D5 (273), polyclonal (277), polyclonal (278), polyclonal (287), polyclonal (298), polyclonal (299), polyclonal (300), G1 (301), G2 (302), J1 (303), TC15 (304), polyclonal (305), polyclonal (306)
Tat Cys-rich domain	polyclonal (274)
Tat basic region	polyclonal (265), TB12 (275), polyclonal (277), polyclonal (278), polyclonal (279), polyclonal (284), polyclonal (287), polyclonal (298), polyclonal (299), polyclonal (300), B1E3 (307), J3B2 (308)
<b>Env (gp160)</b>	
C-HR	polyclonal (1100)
C-domain	polyclonal (669), 5B2 (742), 9G11 (743), TH-Ab1 (744), polyclonal (745), polyclonal (746), polyclonal (747), polyclonal (748)

Binding type	MAb ID (No.)
C-term	105-306 (639), 750-D (641), 158F3 (644), 161D7 (645), 722-D (647), polyclonal (648), 1131-A (650), 858-D (651), 989-D (652), 14D9 (749), 2F5 (750), 4E10 (752), Z13 (753), C8 (757), 1575 (773), polyclonal (777), polyclonal (778), SAR1 (780), 1577 (781), polyclonal (782), 101-342 (1101), 101-451 (1102), 120-1 (1103), T26 (1104), D33 (1105), polyclonal (1106)
Env oligomer	T22 (1232)
Leucine zipper motif	(661), (662)
N-HR	polyclonal (1100)
N-term	polyclonal (670), D33 (1105), 2A2 (1233), AC4 (1234), AD3 (1235), AD3 (1236), ID6 (1237), ID6 (1238)
RT thumb domain	polyclonal (1062)
gp120 C1	M85 (322), 7E2/4 (323), 4D4#85 (324), M92 (325), M86 (326), polyclonal (327), 133/237 (328), 133/290 (329), 133/11 (330), D/3G5 (331), D/6A11 (332), D/5E12 (333), L5.1 (334), 4A7C6 (335), 1D10 (336), B242 (337), 133/192 (338), 489.1(961) (339), 5B3 (340), B10 (341), B2 (342), C6 (343), MF49.1 (344), T1.1 (345), T7.1 (346), T9 (347), GV4D3 (348), B27 (349), B9 (350), B35 (351), D/4B5 (352), D/5A11 (353), D/6B2 (354), B18 (355), B20 (356), MF39.1 (357), 187.2.1 (358), 37.1.1(ARP 327) (359), 6D8 (360), M96 (361), MF119.1 (362), MF4.1 (363), MF53.1 (364), MF58.1 (365), MF77.1 (366), T2.1 (367), 11/65 (368), W1 (369), T11 (370), GV1A8 (371), CA13 (372), 11 (373), 12G10 (374), 135/9 (375), 7C10 (376), C4 (377), MF46.1 (378), 212A (1107), 522-149 (1108), CA1 (1109), L19 (1110), M90 (1111), MAG 104 (1112), MAG 45 (1113), MAG 95 (1114), MAG 97 (1115), P35 (1116), T9 (1117), p7 (1118)
gp120 C1-C2	polyclonal (1057), L100 (1119)
gp120 C1-C4	8.2A (854), EH21 (894), 2/11c (1120), A32 (1121)
gp120 C1-C5	C11 (1122), L81 (1123)
gp120 C2	1006-30-D (418), 847-D (419), 213.1 (423), B12 (424), B13 (425), C13 (426), M89 (427), B21 (428), B23 (429), B24 (430), B25 (431), B3 (432), B26 (433), B29 (434), B36 (435), 110.E (436), 110.C (437)
gp120 C3	B2C (578), 2H1B (581), 2F19C (585), 110.D (586), B32 (587), ICR38.1a (599), polyclonal (1124)
gp120 C4	5C2E5 (594), G3-211 (595), G3-537 (596), ICR38.1a (599), G3-299 (600), G3-42 (601), G3-508 (602), G3-519 (603), G3-536 (604), ICR38.8f (605), MO86/C3 (606), 13H8 (607), G45-60 (608), polyclonal (609), 1662 (610), 1663 (611), 1664 (612), 1697 (613), 1794 (614), 1804 (615), 1807 (616), 1808 (617), 1024 (1125)
gp120 C5	9201 (622), 1C1 (623), 3F5 (624), 5F4/1 (625), 660-178 (626), 9301 (627), B221 (628), H11 (630), W2 (631), M38 (632), 110.1 (635), 42F (636), 43F (637), RV110026 (638), GV1G2 (640), 450-D (642), 670-D (643), 1331A (649), polyclonal (1057), 23A (1127), D7324 (1128)
gp120 CCR5BS	E51 (592), 1.9E (790), 1.9F (791), 2.5E (822), 4.8E (836), 412d (838), 47e (839), E047 (891), ED10 (893), LA15 (919), 17b (1223), 21c (1224)



Binding type	MAB ID (No.)
gp120 CD4BS	JL413 (593), polyclonal (597), 1795 (598), 13a15 (811), 13a23 (812), 13a3 (813), 13a6 (814), 13a7 (815), 13b53 (816), 13b61 (817), 25G (823), 570-D (844), 5E (847), C02-41 (871), C18-2 (874), D02-20 (879), D02-6 (884), F1 (895), m14 (941), m18 (943), m22 (944), m24 (945), polyclonal (1057), D33 (1105), polyclonal (1106), 10/46c (1129), 1008-D (1130), 1027-30-D (1131), 1125H (1132), 1125H (1133), 120-1B1 (1134), 1202-D (1135), 1331E (1136), 1570 (1137), 1595 (1138), 1599 (1139), 15e (1140), 21h (1141), 28A11/B1 (1142), 2G6 (1143), 35F3/E2 (1144), 38G3/A9 (1145), 428 (1146), 448-D (1147), 46D2/D5 (1148), 48-16 (1149), 50-61A (1150), 5145A (1151), 558-D (1152), 559/64-D (1153), 55D5/F9 (1154), 588-D (1155), 654-D (1156), 67G6/C4 (1157), 729-D (1158), 830D (1159), 9CL (1160), BM12 (1161), D20 (1162), D21 (1163), D24 (1164), D25 (1165), D28 (1166), D35 (1167), D39 (1168), D42 (1169), D52 (1170), D53 (1171), D60 (1172), DA48 (1173), DO8i (1174), F105 (1175), F91 (1176), FG39 (1177), Fbb14 (1178), GP13 (1179), GP44 (1180), GP68 (1181), HF1.7 (1182), HT5 (1183), HT6 (1184), HT7 (1185), ICR 39.13g (1186), ICR 39.3b (1187), Ia3 (1188), Ia7 (1189), IgG1b12 (1190), IgGCD4 (1191), L28 (1192), L33 (1193), L41 (1194), L42 (1195), L52 (1196), L72 (1197), M12 (1198), M13 (1199), M6 (1200), MAG 116 (1201), MAG 12B (1202), MAG 29B (1203), MAG 3B (1204), MAG 55 (1205), MAG 72 (1206), MAG 86 (1207), MAG 96 (1208), MTW61D (1209), S1-1 (1210), T13 (1211), T49 (1212), T56 (1213), TH9 (1214), anti-CD4BS summary (1215), b11 (1216), b13 (1217), b14 (1218), b3 (1219), b6 (1220), polyclonal (1221), (1222)
gp120 CD4i	D19 (471), C12 (584), E51 (592), 412d (838), 47e (839), C02-17 (868), C02-19 (869), C02-53 (872), C02-7 (873), D02-1 (878), D02-24 (880), D02-33 (882), D02-34 (883), D02-7 (885), Sb1 (934), m16 (942), polyclonal (1075), (1222), 17b (1223), 21c (1224), 23e (1225), 48d (1226), 49e (1227), Fbb21 (1228), Fbb21 (1229), X5 (1230), 8F101 (1231), 41.1 (1313)
gp120 V1	35D10/D2 (382), 40H2/C7 (383), 43A3/E4 (384), 43C7/B9 (385), 45D1/B7 (386), 46E3/E6 (387), 58E1/B3 (388), 64B9/A6 (389), 69D2/A1 (390), 82D3/C3 (391), polyclonal (618), P3C8 (929)
gp120 V1-V2	polyclonal (1057), 11/68b (1239), 62c (1240), CRA-6 (1241), L15 (1242), T52 (1243), T54 (1244)
gp120 V1-V2 and V3-V5	polyclonal (1245)
gp120 V1-V2-V3	4KG5 (1126)
gp120 V2	6D5 (379), B33 (380), 697-D (392), C108G (394), 11/4c (399), 8.22.2 (400), 12b (401), G3-136 (402), G3-4 (403), polyclonal (618), (1222), 1088 (1246), 110-B (1247), 1357 (1248), 1361 (1249), 1393A (1250), 2158 (1251), 66a (1252), 66c (1253), 684-238 (1254), 830A (1255), CRA-3 (1256), CRA-4 (1257), L17 (1258), SC258 (1259)
gp120 V2-CD4BS	L25 (1260), L39 (1261), L40 (1262), L78 (1263)

Binding type	MAb ID (No.)
gp120 V3	IIIB-V3-26 (438), IIIB-V3-21 (439), 168B8 (440), polyclonal (441), polyclonal (442), MO97/V3 (443), polyclonal (444), 55/11 (445), 8/38c (446), 8/64b (447), polyclonal (448), polyclonal (449), polyclonal (450), polyclonal (451), 9284 (452), polyclonal (453), polyclonal (454), polyclonal (455), polyclonal (456), MAG 109 (457), MAG 49 (458), MAG 53 (459), MAG 56 (460), 1334-D (461), 1324-E (462), polyclonal (463), MO99/V3 (464), C311E (465), 924 (467), polyclonal (468), polyclonal (469), polyclonal (470), D19 (471), 10F10 (472), 2C4 (473), 412-D (474), polyclonal (475), CGP 47 439 (476), polyclonal (477), 178.1 (478), 257-D (479), 311-11-D (480), 41148D (481), 391/95-D (482), Aw (483), Bw (484), DO142-10 (485), Dv (486), Fv (487), Gv (488), Hv (489), polyclonal (490), 50.1 (491), (492), BAT123 (493), 838-D (494), 1006-15D (495), 782-D (496), 908-D (497), 1027-15D (498), F19.26-4 (499), F19.48-3 (500), F19.57-11 (501), 13105100 (502), M77 (503), polyclonal (504), SP.BAL114 (505), SP.SF2:104 (506), polyclonal (507), 19b (508), loop 2 (509), 4G10 (510), 5F7 (511), G3-523 (512), MN215 (513), Nea 9301 (514), 4117C (515), 419-D (516), 453-D (517), 504-D (518), 83.1 (519), 5023B (520), F58/D1 (521), P1/D12 (522), P4/D10 (523), IIIB-13 V3 (524), IIIB-34 V3 (525), A47/B1 (526), D59/A2 (527), G44/H7 (528), MO96/V3 (529), $\mu$ 5.5 (530), $\mu$ 5.5 (531), 268-D (532), 386-D (533), 5042A (534), 5042B (535), 418-D (536), 5021 (537), 5025B (538), 5042 (539), 110.3 (540), 110.4 (541), 110.5 (542), 58.2 (543), KD-247 (545), 537-D (546), 5020 (547), RC25 (548), 5023A (549), 110.6 (550), polyclonal (551), 10/36e (552), 10/54 (553), 11/85b (554), polyclonal (555), 0.5 $\beta$ (556), C $\beta$ 1, 0.5 $\beta$ (557), C25 (558), 447-52D (559), NM-01 (560), 1026 (561), 1034 (562), 59.1 (563), polyclonal (564), 10E3 (565), polyclonal (566), N11-20 (567), 5025A (568), N70-1.9b (569), 902 (570), 694/98-D (571), 9205 (575), 110.I (576), anti-HIV-2 polyclonal (577), IIIB-V3-01 (579), polyclonal (618), 10/540.w (792), 12.19 (804), 12.9 (805), 2601 (824), C02-34 (870), CO11 (877), F2A3 (898), F3.9F (899), F425 B4e8 (901), F425B4a1 (902), LA21 (920), P3E1 (930), PA-1 (933), polyclonal (1057), polyclonal (1060), polyclonal (1065), polyclonal (1084), polyclonal (1090), (1222), (1264), 10D8 (1265), 10F6 (1266), 110.J (1267), 11G5 (1268), 2182 (1269), 2191 (1270), 2219 (1271), 2412 (1272), 2442 (1273), 2456 (1274), 2483 (1275), 2497 (1276), 2557 (1277), 2558 (1278), 2580 (1279), 391/95-D (1280), 39F (1281), 4148d (1282), 55/68b (1283), 5G11 (1284), 6.1 (1285), 6.7 (1286), 8.27.3 (1287), 8E11/A8 (1288), 9305 (1289), A1g8 (1290), AG1121 (1291), Ag1211 (1292), B4a1 (1293), B4e8 (1294), D27 (1295), D47 (1296), D56 (1297), F5.5 (1298), G3-1472 (1299), K24 (1300), TH1 (1301), anti-gp120/V3 (1302), polyclonal (1303), polyclonal (1304), polyclonal (1305), polyclonal (1306), polyclonal (1307), polyclonal (1308), polyclonal (1309), polyclonal (1310), polyclonal (1311), polyclonal (1317)
gp120 V3 discontinuous	11/75a/21/41 (1312), 41.1 (1313), 55/45a/11 (1314)
gp120 V3 mimotope	1108 (1315)
gp120 V3-C4	MO101/V3,C4 (572), polyclonal (1080), polyclonal (1106), polyclonal (1316)
gp120 V3-C5	MO101/V3,C4 (573), MO101/V3,C4 (574)
gp120 V4	D/6D1 (580), 4D7/4 (582), 36.1(ARP 329) (583), C12 (584), polyclonal (588), B15 (589), B34 (590), polyclonal (618), M2 (921), polyclonal (1317)
gp120 V5	polyclonal (618), polyclonal (619)
gp120 V5-C5	CRA1 (620), M91 (621), 8C6/1 (629)
gp120 adjacent to CD4BS	1.4C (788), 1.4G (789), 4.11C (834), 4.6H (835), m9 (947), A32 (1121)
gp120 carbohydrates at glycosylation residues in C2, C3, C4, and V4	2G12 (826)
gp120-CD4 complex	8F101 (1231), 8F102 (1345), CG-10 (1346), CG-25 (1347), CG-4 (1348), CG-76 (1349), CG-9 (1350)

Binding type	MAb ID (No.)
gp41 MPER (membrane proximal external region)	polyclonal (740), polyclonal (746), 14D9 (749), 2F5 (750), Z13e1 (751), 4E10 (752), Z13 (753), 13H11 (810), polyclonal (1075)
gp41 adjacent to cluster II	14D9 (749), 2F5 (750), 13H11 (810)
gp41 alpha-helical hairpin intermediate	98-6 (735), polyclonal (1318)
gp41 cluster I	50-69 (674), 246-D (694), 181-D (697), 240-D (698), F240 (699), D49 (700), D61 (701), T32 (702), T34 (703), 3D6 (730), 1367 (1319), 7B2 (1320)
gp41 cluster II	D50 (732), 98-6 (735), 167-7 (736), ND-15G1 (737), 167-D (738), 126-6 (1321), 1342 (1322), 1379 (1323), 2.2B (1324), Fab D11 (1325), Fab D5 (1326), Fab G1 (1327), Fab M10 (1328), Fab M12 (1329), Fab M15 (1330), Fab S10 (1331), Fab S6 (1332), Fab S8 (1333), Fab S9 (1334), Fab T3 (1335), Md-1 (1336), 1281 (1343)
gp41 cluster III	Fab A9 (1337), Fab G15 (1338), Fab G5 (1339), Fab L1 (1340), Fab L11 (1341), Fab L2 (1342)
gp41 cytoplasmic domain	Chessie 8 (1344)
gp41 internal trimeric coiled-coil of N-helices	1034 (801), 1492 (818)
gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices	1010 (793), 1018 (795), 1020 (798), 1022 (799)
gp41 six-helix bundle immunodominant region	167-D (738), 1014 (794), 1019 (796), polyclonal (1100), 1281 (1343), NC-1 (1356)
p24+gp41 quaternary structure	3D6 (730), 105-518 (1351)
<b>Nef</b>	31A1 (1352), 39A64 (1353), 39B86 (1354), 9303 (1355)
C-term	2909 (825)
<b>HIV-1</b>	AE6 (1401), AG11 (1402), EH1 (1403), AE6 (1411)
gp120 C1	13b23 (1416)
gp120 CCR5BS	LA28 (1417), LF17 (1418)
gp120 CD4BS	13b18 (1415)
gp120 V3	polyclonal (1428)

## IV-B-2 Alphabetical listing of MABs

Cross reference of MAb names and their order of appearance in the tables. Alphanumeric sorting is symbols, digits and letters.		1027-15D	498	12-B-4	103	14D9	749
		1027-30-D	1131	12.19	804	15-21	33
		1034	562	12.9	805	1570	1137
		1034	801	120-1	1103	1575	773
		105-134	802	120-16	734	1576	760
		105-306	639	120-1B1	1134	1577	781
		105-518	1351	1202-D	1135	1578	761
		288	729	126-50	806	1579	762
		492	117	126-6	1321	1583	763
		661	111	1281	1343	158F3	644
		662	1246	12b	401	1595	1138
		671	1265	12G-A8g2	20	1599	1139
		784	565	12G-D7h11	21	15e	1140
		785	179	12G-H1c7	22	15F8C7	46
		786	803	12G10	374	16	232
		787	472	12H-D3b3	19	16/4/2	135
		1222	1266	12H2	807	161D7	645
		1264	373	12I-D12g2	23	1662	610
		1412	62	13	230	1663	611
		1413	396	13-102-100	77	1664	612
		1414	397	13.10	808	167-7	736
		0.5β	399	13/035	1360	167-D	738
		1-B-7	368	13/042	1359	168B8	440
		1-E-4	1239	13/058	1372	1696	178
		1-E-9	1312	13105100	502	1697	613
		1.152 B3	554	1324-E	462	17	213
		1.153 G10	1247	133/11	330	178.1	478
		1.158 E2	414	133/192	338	1794	614
		1.160 B3	635	133/237	328	1795	598
		1.17.3	540	133/290	329	17b	1223
		1.2	541	1331-D	809	1804	615
		1.4C	542	1331A	649	1807	616
		1.4G	550	1331E	1136	1808	617
		1.9E	437	1334-D	461	181-D	697
		1.9F	586	1342	1322	183-H12-5C	136
		10-E-7	436	135/9	375	187.2.1	358
		10-G-9	576	1357	1248	1899	764
		10.1	1267	1361	1249	19	220
		10/36e	112	1367	1319	1907	765
		10/46c	1315	1379	1323	1908	766
		10/54	50	1393A	1250	1909	767
		10/540.w	47	13a15	811	19b	508
		10/76b	56	13a23	812	1A1	653
		1006-15D	37	13a3	813	1A7	91
		1006-30-D	38	13a6	814	1B1	819
		1008-D	39	13a7	815	1B2C12	87
		101-342	1132	13b18	1415	1B8.env	718
		101-451	1133	13b23	1416	1C1	623
		1010	57	13B5	116	1C12B1	233
		1014	75	13b53	816	1C4	202
		1018	650	13b61	817	1D10	336
		1019	704	13E1	181	1D10	820
		102-135	106	13H11	810	1D2F11	280
		1020	107	13H8	607	1D4A3	197
		1022	1268	14	231	1D9	29
		1024	26	1492	818	1D9D5	273
		1025	229	14D4E11	51	1E8	185
		1026					

## Alphabetical listing of MABs

## Cross Reference Listing of MABs

1F11	663	2E4	1395	3D9	665	4B3	666
1F6	92	2F11	693	3E11	13	4B4C4	282
1F7	821	2F19C	585	3E11	205	4C11.D8	412
1G10	317	2F2	1390	3E6	1392	4C9	30
1G5C8	52	2F5	750	3F10	238	4D4	667
1G7	318	2G12	826	3F2	1367	4D4#85	324
1H5	664	2G2	320	3F5	624	4D6	214
2-19	221	2G6	1143	3F9	206	4D7/4	582
2-E-4	63	2H12	1396	3G12	1371	4E10	752
2-H-4	64	2H1B	581	3G4	316	4F6	216
2.2B	1324	3-B-7	70	3H3E	1405	4G10	510
2.5E	822	3-H-7	27	3H6	312	4G2	668
2/11c	1120	30:3E5	84	3H6	833	4G9	309
21	234	30D	827	4	239	4H2B1	31
212A	1107	31-11	34	4	722	4H4	1357
213.1	423	31/03	1378	4-20	223	4KG5	1126
2158	1251	311-11-D	480	4.11C	834	5-21-3	733
2182	1269	31710B	828	4.6H	835	50-61A	1150
2191	1270	31A1	1352	4.8E	836	50-69	674
21c	1224	31D6	189	406/01	79	50.1	491
21h	1141	31G8	190	40D3/C11	837	5020	547
2219	1271	32	235	40H2/C7	383	5021	537
23A	1127	32/1.24.89	11	41-1	677	5023A	549
23A5G4	93	32/5.8.42	3	41-1	768	5023B	520
23A5G5	94	32/5.8.42	4	41-2	769	5025A	568
23e	1225	322-151	410	41-3	770	5025B	538
240-D	698	32:32K	113	41-6	723	504-D	518
241-D	137	32E7	191	41-7	724	5042	539
2412	1272	33	254	41.1	1313	5042A	534
2442	1273	33D5	192	41.4	678	5042B	535
2456	1274	35	236	41148D	481	5145A	1151
246-D	694	35D10/D2	382	4117C	515	522-149	1108
2483	1275	35F3/E2	1144	412-D	474	52G5/B9	841
2497	1276	36.1(ARP 329)	583	412d	838	537-D	546
24G3	654	37.1.1(ARP 327)	359	4148d	1282	55/11	445
25.3	76	38/12b	407	418-D	536	55/45a/11	1314
25/03	1365	38/60b	408	419-D	516	55/68b	1283
2557	1277	386-D	533	41S-2	756	558-D	1152
2558	1278	38:9.6K	81	428	1146	559/64-D	1153
257-D	479	38B5/C9	829	42F	636	55D5/F9	1154
2580	1279	38G3/A9	1145	43A3/E4	384	55E4/H1	842
25C2	655	391/95-D	482	43C7/B9	385	56C4/C8	843
25G	823	391/95-D	1280	43F	637	570-D	844
26/028	1373	39A64	1353	447-52D	559	57B6/F1	845
26/76	1366	39B86	1354	448-D	1147	57H5/D7	846
2601	824	39F	1281	450-D	642	58.2	543
268-D	532	39H10/A11	830	453-D	517	588-D	1155
28A11/B1	1142	3A2	1397	45D1/B7	386	58E1/B3	388
2909	825	3A6	36	46D2/D5	1148	59.1	563
2A2	1233	3B10	12	46E3/E6	387	5B11	240
2A2/26	673	3B4B	1404	47-2	53	5B2	193
2A3	1394	3C9	831	47e	839	5B2	742
2A6	138	3D10G6	95	48-16	1149	5B3	340
2C11	203	3D12	237	489.1(961)	339	5C2E5	594
2C4	473	3D12	1368	48d	1226	5D9	218
2D9D5	297	3D3	44	493-156	413	5E	847
2D9E7	281	3D3.B8	411	49B11/A1	840	5E2.A3k	139
2E3	204	3D5	832	49e	1227	5F	257
2E3	1375	3D6	730	4A7C6	335	5F3	656

Cross Reference Listing of MABs

Alphabetical listing of MABs

5F4/1	625	7F11	226	9G2	314	B3	432
5F7	511	7F11	591	9G5	32	b3	1219
5F8	207	8-22	222	9G5A	696	B30	754
5G	258	8-6	219	$\alpha(566-586)$	657	B31	758
5G11	1284	8-D-2	65	$\mu 5.5$	530	B32	587
5G7D8	283	8-D-5	73	$\mu 5.5$	531	B33	380
6-19	224	8-G-9	66	A1g8	1290	B33	759
6-D-12	71	8-H-7	67	A32	1121	B34	590
6-E-7	72	8.22.2	400	A47/B1	526	B35	351
6.1	1285	8.27.3	1287	A6	1361	B36	435
6.1	1406	8.2A	854	A7	1364	B4	862
6.7	1286	8/38c	446	A9	858	B4a1	1293
60b	405	8/64b	447	Ab2	310	B4e8	1294
62c	1240	82D3/C3	391	Ab3	319	B4f8	17
63G4/E2	848	83.1	519	Ab4	315	B5	863
64B9/A6	389	830A	1255	AC2	144	B6	864
654-D	1156	830D	1159	AC4	1234	b6	1220
65B12/C5	849	838-D	494	AD2	127	B8	779
660-178	626	847-D	419	AD3	1235	B9	350
66a	1252	858-D	651	AD3	1236	BAT085	404
66c	1253	85G11/D8	855	ADP421 polyclonal	859	BAT123	493
670-D	643	86	686	AE6	1401	BAT267	865
67G6/C4	1157	87E4/A8	856	AE6	1411	BAT401	866
68.1	725	88-158/02	774	AG10H9	860	BAT509	867
68.11	726	88-158/022	775	AG11	1402	BC1071	145
684-238	1254	88-158/079	776	AG1121	1291	BE10	146
694/98-D	571	8B11	182	Ag1211	1292	BE3	109
694/98D	850	8C10	183	AH48	861	BM12	1161
697-D	392	8C6/1	629	AM5C6	1362	Bw	484
69D2/A1	390	8E11/A8	1288	AM5C6	1363	C02-17	868
6B10	241	8E5	227	anti-HIV-1 RT	249	C02-19	869
6B9	242	8E7	313	anti-HIV-2 polyclonal	577	C02-34	870
6B9	256	8F101	1231	anti-CD4BS summary	1215	C02-41	871
6C4/S	393	8F102	1345	anti-gp120/V3	1302	C02-53	872
6C5	211	8G4	212	anti-K159	217	C02-7	873
6D5	379	8G5	184	anti-P1	690	C108G	394
6D8	360	8H10	15	anti-p24	156	C11	1122
6D8	851	9-11	675	Aw	483	C12	584
6E10	852	902	570	B10	341	C13	426
6E9	243	907	466	b11	1216	C18-2	874
6G5	208	908-D	497	B12	424	C2003	201
7-1054	853	91-5	49	B13	425	C25	558
7-16	215	91-6	141	b13	1217	C31	875
71-31	140	9201	622	b14	1218	C311E	465
714/01	54	9205	575	B15	589	C4	377
722-D	647	924	467	B18	355	C5122	104
729-D	1158	9284	452	B1E3	307	C5123	68
74	406	9301	627	B2	342	C5126	28
75	727	9303	1355	B20	356	C5200	114
750-D	641	9305	1289	B21	428	C6	343
782-D	496	97B1/E8	857	B221	628	C8	757
7B2	1320	98-4.3	142	B23	429	C $\beta$ 1, 0.5 $\beta$	557
7B6	209	98-4.9	143	B24	430	CA1	1109
7C10	376	98-43	676	B242	337	CA13	372
7C3	225	98-6	735	B25	431	CA5	128
7C4	244	989-D	652	B26	433	CB-13/5	42
7C4	259	9A4C4	105	B27	349	CD-4/1	45
7C6	210	9CL	1160	B29	434	CD12B4	108
7E2/4	323	9G11	743	B2C	578	CD9	147

## Alphabetical listing of MABs

CG-10	1346	DF3	129	Fab G1	1327	HF1.7	1182
CG-25	1347	DG8	124	Fab G15	1338	HH3	126
CG-4	1348	DO142-10	485	Fab G5	1339	HIVIG	912
CG-76	1349	DO8i	1174	Fab L1	1340	HT5	1183
CG-9	1350	Dv	486	Fab L11	1341	HT6	1184
CGP 47 439	476	DZ	783	Fab L2	1342	HT7	1185
CH9B2	148	E-4	245	Fab L9	906	human sera	157
Chessie 8	1344	E047	891	Fab M10	1328	Hv	489
Chim 1	633	E2E	892	Fab M12	1329	HyHIV-1	5
clone 3	721	E5	1393	Fab M12B	681	HyHIV-15	25
CM51	876	E51	592	Fab M15	1330	HyHIV-19	153
CO11	877	E7	1400	Fab M26B	682	HyHIV-2	6
CRA-3	1256	E9	1391	Fab M8B	683	HyHIV-21	16
CRA-4	1257	EB1A9	82	Fab S10	1331	HyHIV-22	18
CRA-6	1241	EB5	125	Fab S6	1332	HyHIV-3	7
CRA1	620	EC3	130	Fab S8	1333	HyHIV-4	8
D/3G5	331	EC6	122	Fab S9	1334	HyHIV-5	9
D/4B5	352	ED10	893	Fab T2	684	HyHIV-6	10
D/5A11	353	ED6	771	Fab T3	1335	i5B11	121
D/5E12	333	ED8	149	Fbb14	1178	Ia3	1188
D/6A11	332	EF7	85	Fbb21	1228	Ia7	1189
D/6B2	354	EH1	1403	Fbb21	1229	ICR 39.13g	1186
D/6D1	580	EH12E1	150	FC12	131	ICR 39.3b	1187
D02-1	878	EH21	894	FF1	74	ICR38.1a	599
D02-20	879	F-6	255	FG39	1177	ICR38.8f	605
D02-24	880	F1	895	FH2	115	ID6	1237
D02-3	881	F1	1389	Fv	487	ID6	1238
D02-33	882	F105	1175	G1	301	ID8F6	40
D02-34	883	F11.2.32	180	G11G1	151	IE8G2	154
D02-6	884	F14.11	1377	G11H3	152	IgA6/30λ	914
D02-7	885	F172-D8	731	G12	907	IgA6/5k	915
D1	886	F19.26-4	499	G2	302	IgA6/L4	916
D12	887	F19.48-3	500	G2	908	IgG1b12	1190
D16	888	F19.57-11	501	G3-136	402	IgGCD4	1191
D19	471	F2	1382	G3-1472	1299	IIIB-13 V3	524
D20	1162	F223	896	G3-211	595	IIIB-34 V3	525
D21	1163	F240	699	G3-299	600	IIIB-V3-01	579
D24	1164	F285	897	G3-4	403	IIIB-V3-21	439
D25	1165	F2A3	898	G3-42	601	IIIB-V3-26	438
D27	1295	F3	1386	G3-508	602	IVI-4G6	913
D28	1166	F3.9F	899	G3-519	603	J1	303
D33	1105	F4	1381	G3-523	512	J1	416
D35	1167	F424	900	G3-536	604	J3	417
D39	1168	F425 B4e8	901	G3-537	596	J3B2	308
D4	889	F425B4a1	902	G44/H7	528	J4	262
D42	1169	F5-2	41	G45-60	608	JB7	133
D43	890	F5-4	97	GE4	132	JF11	134
D47	1296	F5.5	1298	GP13	1179	JL413	593
D49	700	F58/D1	521	GP44	1180	K14	917
D50	732	F7	903	GP68	1181	K24	1300
D52	1170	F8	1387	Gv	488	KD-247	545
D53	1171	F91	1176	GV1A8	371	KU32	918
D56	1297	Fab A1	679	GV1G2	640	L-anti-Tat	289
D59/A2	527	Fab A12	904	GV4D3	348	L100	1119
D60	1172	Fab A2	905	GV4H3	415	L14	110
D61	701	Fab A4	680	H11	630	L14.17	1
D7324	1128	Fab A9	1337	H2	909	L15	1242
DA48	1173	Fab D11	1325	H8	910	L17	1258
DE7	321	Fab D5	1326	HBW4	911	L19	1110

Cross Reference Listing of MABs

Alphabetical listing of MABs

L25	1260	MAB 35	228	NM-01	560	polyclonal	285
L28	1192	MAG 104	1112	NT2/4D5.24	286	polyclonal	287
L33	1193	MAG 109	457	NT3/2D1.1	271	polyclonal	290
L39	1261	MAG 116	1201	P1/D12	522	polyclonal	291
L40	1262	MAG 12B	1202	P35	1116	polyclonal	292
L41	1194	MAG 29B	1203	P3C8	929	polyclonal	293
L42	1195	MAG 3B	1204	P3E1	930	polyclonal	294
L5.1	334	MAG 45	1113	P4/D10	523	polyclonal	295
L52	1196	MAG 49	458	P43110	931	polyclonal	296
L72	1197	MAG 53	459	P5-3	932	polyclonal	298
L78	1263	MAG 55	1205	p7	1118	polyclonal	299
L81	1123	MAG 56	460	PA-1	933	polyclonal	300
LA15	919	MAG 6B	923	PC5009	658	polyclonal	305
LA21	920	MAG 72	1206	polyclonal	2	polyclonal	306
LA28	1417	MAG 86	1207	polyclonal	14	polyclonal	327
LA9 (121-134)	772	MAG 95	1114	polyclonal	24	polyclonal	381
LF17	1418	MAG 96	1208	polyclonal	43	polyclonal	409
LH-104-A	89	MAG 97	1115	polyclonal	48	polyclonal	441
LH-104-B	118	Md-1	1336	polyclonal	55	polyclonal	442
LH-104-C	102	MF119.1	362	polyclonal	80	polyclonal	444
LH-104-E	86	MF169.1	420	polyclonal	83	polyclonal	448
LH-104-G	120	MF170.1	421	polyclonal	96	polyclonal	449
LH-104-I	119	MF39.1	357	polyclonal	158	polyclonal	450
LH-104-K	88	MF4.1	363	polyclonal	159	polyclonal	451
loop 2	509	MF46.1	378	polyclonal	160	polyclonal	453
M-1	705	MF49.1	344	polyclonal	161	polyclonal	454
M-11	706	MF53.1	364	polyclonal	162	polyclonal	455
M-13	707	MF58.1	365	polyclonal	163	polyclonal	456
M-2	708	MF77.1	366	polyclonal	164	polyclonal	463
M-22	709	MF87.1	422	polyclonal	165	polyclonal	468
M-24	710	MN215	513	polyclonal	166	polyclonal	469
M-25	711	MO101/V3,C4	572	polyclonal	167	polyclonal	470
M-28	712	MO101/V3,C4	573	polyclonal	168	polyclonal	475
M-29	713	MO101/V3,C4	574	polyclonal	169	polyclonal	477
M-36	714	MO28	924	polyclonal	170	polyclonal	490
M-4	715	MO30	925	polyclonal	171	polyclonal	504
M-6	716	MO43	926	polyclonal	172	polyclonal	507
M12	123	MO86/C3	606	polyclonal	173	polyclonal	544
M12	1198	MO9.42.2	98	polyclonal	174	polyclonal	551
M13	1199	MO9.50.2	99	polyclonal	175	polyclonal	555
m14	941	MO96/V3	529	polyclonal	176	polyclonal	564
m16	942	MO97/V3	443	polyclonal	186	polyclonal	566
m18	943	MO99/V3	464	polyclonal	194	polyclonal	588
M2	921	MTW61D	1209	polyclonal	200	polyclonal	597
m22	944	multiple Fabs	948	polyclonal	250	polyclonal	609
m24	945	multiple MABs	949	polyclonal	251	polyclonal	618
M25	922	multiple MABs	950	polyclonal	252	polyclonal	619
M38	632	multiple MABs	951	polyclonal	253	polyclonal	634
m46	946	N11-20	567	polyclonal	263	polyclonal	646
M6	1200	N2-4	927	polyclonal	264	polyclonal	648
M77	503	N70-1.9b	569	polyclonal	265	polyclonal	660
M85	322	N70-2.3a	928	polyclonal	266	polyclonal	669
M86	326	NC-1	1356	polyclonal	270	polyclonal	670
M89	427	ND-15G1	737	polyclonal	274	polyclonal	672
m9	947	Nea 9301	514	polyclonal	276	polyclonal	685
M90	1111	NF1A1	1398	polyclonal	277	polyclonal	687
M91	621	NF2B2	1407	polyclonal	278	polyclonal	689
M92	325	NF3A3	1408	polyclonal	279	polyclonal	691
M96	361	NF8B4	1409	polyclonal	284	polyclonal	692



## Alphabetical listing of MAbs

## Cross Reference Listing of MAbs

polyclonal	695	polyclonal	996	polyclonal	1055	polyclonal	1316
polyclonal	719	polyclonal	997	polyclonal	1056	polyclonal	1317
polyclonal	720	polyclonal	998	polyclonal	1057	polyclonal	1318
polyclonal	728	polyclonal	999	polyclonal	1058	polyclonal	1358
polyclonal	739	polyclonal	1000	polyclonal	1059	polyclonal	1369
polyclonal	740	polyclonal	1001	polyclonal	1060	polyclonal	1370
polyclonal	741	polyclonal	1002	polyclonal	1061	polyclonal	1374
polyclonal	745	polyclonal	1003	polyclonal	1062	polyclonal	1376
polyclonal	746	polyclonal	1004	polyclonal	1063	polyclonal	1379
polyclonal	747	polyclonal	1005	polyclonal	1064	polyclonal	1380
polyclonal	748	polyclonal	1006	polyclonal	1065	polyclonal	1383
polyclonal	755	polyclonal	1007	polyclonal	1066	polyclonal	1384
polyclonal	777	polyclonal	1008	polyclonal	1067	polyclonal	1385
polyclonal	778	polyclonal	1009	polyclonal	1068	polyclonal	1388
polyclonal	782	polyclonal	1010	polyclonal	1069	polyclonal	1399
polyclonal	952	polyclonal	1011	polyclonal	1070	polyclonal	1410
polyclonal	953	polyclonal	1012	polyclonal	1071	polyclonal	1419
polyclonal	954	polyclonal	1013	polyclonal	1072	polyclonal	1420
polyclonal	955	polyclonal	1014	polyclonal	1073	polyclonal	1421
polyclonal	956	polyclonal	1015	polyclonal	1074	polyclonal	1422
polyclonal	957	polyclonal	1016	polyclonal	1075	polyclonal	1423
polyclonal	958	polyclonal	1017	polyclonal	1076	polyclonal	1424
polyclonal	959	polyclonal	1018	polyclonal	1077	polyclonal	1425
polyclonal	960	polyclonal	1019	polyclonal	1078	polyclonal	1426
polyclonal	961	polyclonal	1020	polyclonal	1079	polyclonal	1427
polyclonal	962	polyclonal	1021	polyclonal	1080	polyclonal	1428
polyclonal	963	polyclonal	1022	polyclonal	1081	polyclonal	1429
polyclonal	964	polyclonal	1023	polyclonal	1082	polyclonal	1430
polyclonal	965	polyclonal	1024	polyclonal	1083	polyclonal	1431
polyclonal	966	polyclonal	1025	polyclonal	1084	polyclonal	1432
polyclonal	967	polyclonal	1026	polyclonal	1085	polyclonal	1433
polyclonal	968	polyclonal	1027	polyclonal	1086	polyclonal	1434
polyclonal	969	polyclonal	1028	polyclonal	1087	polyclonal	1435
polyclonal	970	polyclonal	1029	polyclonal	1088	polyclonal	1436
polyclonal	971	polyclonal	1030	polyclonal	1089	polyclonal	1437
polyclonal	972	polyclonal	1031	polyclonal	1090	polyclonal	1438
polyclonal	973	polyclonal	1032	polyclonal	1091	polyclonal	1439
polyclonal	974	polyclonal	1033	polyclonal	1092	polyclonal	1440
polyclonal	975	polyclonal	1034	polyclonal	1093	polyclonal	1441
polyclonal	976	polyclonal	1035	polyclonal	1094	polyclonal	1442
polyclonal	977	polyclonal	1036	polyclonal	1095	polyclonal	1443
polyclonal	978	polyclonal	1037	polyclonal	1096	polyclonal	1444
polyclonal	979	polyclonal	1038	polyclonal	1097	polyclonal	1445
polyclonal	980	polyclonal	1039	polyclonal	1098	polyclonal	1446
polyclonal	981	polyclonal	1040	polyclonal	1099	polyclonal	1447
polyclonal	982	polyclonal	1041	polyclonal	1100	polyclonal	1448
polyclonal	983	polyclonal	1042	polyclonal	1106	polyclonal $\alpha$ 577-596	659
polyclonal	984	polyclonal	1043	polyclonal	1124	polyclonal $\alpha$ 598-609	717
polyclonal	985	polyclonal	1044	polyclonal	1221	polyclonal HIVIG	177
polyclonal	986	polyclonal	1045	polyclonal	1245	RC25	548
polyclonal	987	polyclonal	1046	polyclonal	1303	RL4.72.1	78
polyclonal	988	polyclonal	1047	polyclonal	1304	RSD-33	398
polyclonal	989	polyclonal	1048	polyclonal	1305	RT-4	246
polyclonal	990	polyclonal	1049	polyclonal	1306	RT6H	198
polyclonal	991	polyclonal	1050	polyclonal	1307	RT7O	247
polyclonal	992	polyclonal	1051	polyclonal	1308	RT7U	248
polyclonal	993	polyclonal	1052	polyclonal	1309	RTMAb8	196
polyclonal	994	polyclonal	1053	polyclonal	1310	RV110026	638
polyclonal	995	polyclonal	1054	polyclonal	1311	S1-1	1210

## Cross Reference Listing of MAbs

## Alphabetical listing of MAbs

SAR1	780
Sb1	934
sc-FV p17	35
SC258	1259
SP.BAL114	505
SP.SF2:104	506
T1.1	345
T11	370
T13	1211
T15G1	935
T2.1	367
T20	936
T22	1232
T26	1104
T27	937
T3	938
T30	939
T32	702
T34	703
T4	940
T49	1212
T52	1243
T54	1244
T56	1213
T7.1	346
T9	347
T9	1117
TA9	267
TB12	275
TC15	304
TD84	268
TE135	269
TG001	261
TG002	260
TH-Ab1	744
TH1	1301
TH9	1214
V10	100
V10-9	688
V107	101
V7-8	155
W1	369
W2	631
X5	1230
Z13	753
Z13e1	751

IV-B-3 MABs by order of appearance in tables

<b>No.</b>	<b>MAB ID</b>	54	714/01	111	108/03	165	polyclonal
<b>p17</b>		55	polyclonal	112	110/015	166	polyclonal
1	L14.17	56	111/073	113	32:32K	167	polyclonal
2	polyclonal	57	113/038	114	C5200	168	polyclonal
3	32/5.8.42	58	1-E-4	115	FH2	169	polyclonal
4	32/5.8.42	59	1-E-9	116	13B5	170	polyclonal
5	HyHIV-1	60	10-E-7	117	106/01	171	polyclonal
6	HyHIV-2	61	10-G-9	118	LH-104-B	172	polyclonal
7	HyHIV-3	62	11-C-5	119	LH-104-I	173	polyclonal
8	HyHIV-4	63	2-E-4		<b>p24-p2p7p1p6</b>	174	polyclonal
9	HyHIV-5	64	2-H-4	120	LH-104-G	175	polyclonal
10	HyHIV-6	65	8-D-2		<b>p2p7p1p6</b>	176	polyclonal
11	32/1.24.89	66	8-G-9	121	i5B11	177	polyclonal HIVIG
12	3B10	67	8-H-7	122	EC6		<b>Protease</b>
13	3E11	68	C5123	123	M12	178	1696
14	polyclonal	69	1-B-7	124	DG8	179	10E7
15	8H10	70	3-B-7	125	EB5	180	F11.2.32
16	HyHIV-21	71	6-D-12	126	HH3	181	13E1
17	B4f8	72	6-E-7	127	AD2	182	8B11
18	HyHIV-22	73	8-D-5	128	CA5	183	8C10
19	12H-D3b3	74	FF1	129	DF3	184	8G5
20	12G-A8g2	75	113/072	130	EC3		<b>RT</b>
21	12G-D7h11	76	25.3	131	FC12	185	1E8
22	12G-H1c7	77	13-102-100	132	GE4	186	polyclonal
23	12I-D12g2	78	RL4.72.1	133	JB7	187	1.152 B3
24	polyclonal	79	406/01	134	JF11	188	1.158 E2
25	HyHIV-15	80	polyclonal		<b>Gag</b>	189	31D6
26	11H9	81	38:9.6K	135	16/4/2	190	31G8
27	3-H-7	82	EB1A9	136	183-H12-5C	191	32E7
28	C5126	83	polyclonal	137	241-D	192	33D5
29	1D9	84	30:3E5	138	2A6	193	5B2
30	4C9	85	EF7	139	5E2.A3k	194	polyclonal
31	4H2B1	86	LH-104-E	140	71-31	195	1.153 G10
32	9G5	87	1B2C12	141	91-6	196	RTMAb8
33	15-21	88	LH-104-K	142	98-4.3	197	1D4A3
34	31-11	89	LH-104-A	143	98-4.9	198	RT6H
35	sc-FV p17	90	1.17.3	144	AC2	199	1.160 B3
	<b>p17-p24</b>	91	1A7	145	BC1071	200	polyclonal
36	3A6	92	1F6	146	BE10	201	C2003
	<b>p24</b>	93	23A5G4	147	CD9		<b>Integrase</b>
37	111/182	94	23A5G5	148	CH9B2	202	1C4
38	112/021	95	3D10G6	149	ED8	203	2C11
39	112/047	96	polyclonal	150	EH12E1	204	2E3
40	ID8F6	97	F5-4	151	G11G1	205	3E11
41	F5-2	98	MO9.42.2	152	G11H3	206	3F9
42	CB-13/5	99	MO9.50.2	153	HyHIV-19	207	5F8
43	polyclonal	100	V10	154	IE8G2	208	6G5
44	3D3	101	V107	155	V7-8	209	7B6
45	CD-4/1	102	LH-104-C	156	anti-p24	210	7C6
46	15F8C7	103	12-B-4	157	human sera	211	6C5
47	111/052	104	C5122	158	polyclonal	212	8G4
48	polyclonal	105	9A4C4	159	polyclonal	213	17
49	91-5	106	11C10B10	160	polyclonal	214	4D6
50	1109/01	107	11D11F2	161	polyclonal	215	7-16
51	14D4E11	108	CD12B4	162	polyclonal	216	4F6
52	1G5C8	109	BE3	163	polyclonal	217	anti-K159
53	47-2	110	L14	164	polyclonal	218	5D9

Cross Reference Listing of MAbs

MAbs by order of appearance in tables

219	8-6	274	polyclonal	330	133/11	389	64B9/A6
220	19	275	TB12	331	D/3G5	390	69D2/A1
221	2-19	276	polyclonal	332	D/6A11	391	82D3/C3
222	8-22	277	polyclonal	333	D/5E12	392	697-D
223	4-20	278	polyclonal	334	L5.1	393	6C4/S
224	6-19	279	polyclonal	335	4A7C6	394	C108G
225	7C3	280	1D2F11	336	1D10	395	10/76b
226	7F11	281	2D9E7	337	B242	396	11/41e
227	8E5	282	4B4C4	338	133/192	397	11/4b
228	MAB 35	283	5G7D8	339	489.1(961)	398	RSD-33
<b>Pol</b>		284	polyclonal	340	5B3	399	11/4c
229	12	285	polyclonal	341	B10	400	8.22.2
230	13	286	NT2/4D5.24	342	B2	401	12b
231	14	287	polyclonal	343	C6	402	G3-136
232	16	288		344	MF49.1	403	G3-4
233	1C12B1	289	L-anti-Tat	345	T1.1	404	BAT085
234	21	290	polyclonal	346	T7.1	405	60b
235	32	291	polyclonal	347	T9	406	74
236	35	292	polyclonal	348	GV4D3	407	38/12b
237	3D12	293	polyclonal	349	B27	408	38/60b
238	3F10	294	polyclonal	350	B9	409	polyclonal
239	4	295	polyclonal	351	B35	410	322-151
240	5B11	296	polyclonal	352	D/4B5	411	3D3.B8
241	6B10	297	2D9D5	353	D/5A11	412	4C11.D8
242	6B9	298	polyclonal	354	D/6B2	413	493-156
243	6E9	299	polyclonal	355	B18	414	110.1
244	7C4	300	polyclonal	356	B20	415	GV4H3
245	E-4	301	G1	357	MF39.1	416	J1
246	RT-4	302	G2	358	187.2.1	417	J3
247	RT7O	303	J1	359	37.1.1(ARP 327)	418	1006-30-D
248	RT7U	304	TC15	360	6D8	419	847-D
249	anti-HIV-1 RT	305	polyclonal	361	M96	420	MF169.1
250	polyclonal	306	polyclonal	362	MF119.1	421	MF170.1
251	polyclonal	307	B1E3	363	MF4.1	422	MF87.1
252	polyclonal	308	J3B2	364	MF53.1	423	213.1
253	polyclonal	<b>Rev</b>		365	MF58.1	424	B12
254	33	309	4G9	366	MF77.1	425	B13
255	F-6	310	Ab2	367	T2.1	426	C13
256	6B9	311	10.1	368	11/65	427	M89
257	5F	312	3H6	369	W1	428	B21
258	5G	313	8E7	370	T11	429	B23
259	7C4	314	9G2	371	GV1A8	430	B24
<b>Vif</b>		315	Ab4	372	CA13	431	B25
260	TG002	316	3G4	373	11	432	B3
261	TG001	317	1G10	374	12G10	433	B26
262	J4	318	1G7	375	135/9	434	B29
263	polyclonal	319	Ab3	376	7C10	435	B36
<b>Vpr</b>		320	2G2	377	C4	436	110.E
264	polyclonal	<b>Vpu</b>		378	MF46.1	437	110.C
<b>Tat</b>		321	DE7	379	6D5	438	IIIB-V3-26
265	polyclonal	<b>gp160</b>		380	B33	439	IIIB-V3-21
266	polyclonal	322	M85	381	polyclonal	440	168B8
267	TA9	323	7E2/4	382	35D10/D2	441	polyclonal
268	TD84	324	4D4#85	383	40H2/C7	442	polyclonal
269	TE135	325	M92	384	43A3/E4	443	MO97/V3
270	polyclonal	326	M86	385	43C7/B9	444	polyclonal
271	NT3/2D1.1	327	polyclonal	386	45D1/B7	445	55/11
272	1.2	328	133/237	387	46E3/E6	446	8/38c
273	1D9D5	329	133/290	388	58E1/B3	447	8/64b

**MAbs by order of appearance in tables**

**Cross Reference Listing of MAbs**

448	polyclonal	507	polyclonal	566	polyclonal	625	5F4/1
449	polyclonal	508	19b	567	N11-20	626	660-178
450	polyclonal	509	loop 2	568	5025A	627	9301
451	polyclonal	510	4G10	569	N70-1.9b	628	B221
452	9284	511	5F7	570	902	629	8C6/1
453	polyclonal	512	G3-523	571	694/98-D	630	H11
454	polyclonal	513	MN215	572	MO101/V3,C4	631	W2
455	polyclonal	514	Nea 9301	573	MO101/V3,C4	632	M38
456	polyclonal	515	4117C	574	MO101/V3,C4	633	Chim 1
457	MAG 109	516	419-D	575	9205	634	polyclonal
458	MAG 49	517	453-D	576	110.I	635	110.1
459	MAG 53	518	504-D	577	anti-HIV-2 polyclonal	636	42F
460	MAG 56	519	83.1	578	B2C	637	43F
461	1334-D	520	5023B	579	IIIB-V3-01	638	RV110026
462	1324-E	521	F58/D1	580	D/6D1	639	105-306
463	polyclonal	522	P1/D12	581	2H1B	640	GV1G2
464	MO99/V3	523	P4/D10	582	4D7/4	641	750-D
465	C311E	524	IIIB-13 V3	583	36.1(ARP 329)	642	450-D
466	907	525	IIIB-34 V3	584	C12	643	670-D
467	924	526	A47/B1	585	2F19C	644	158F3
468	polyclonal	527	D59/A2	586	110.D	645	161D7
469	polyclonal	528	G44/H7	587	B32	646	polyclonal
470	polyclonal	529	MO96/V3	588	polyclonal	647	722-D
471	D19	530	μ5.5	589	B15	648	polyclonal
472	10F10	531	μ5.5	590	B34	649	1331A
473	2C4	532	268-D	591	7F11	650	1131-A
474	412-D	533	386-D	592	E51	651	858-D
475	polyclonal	534	5042A	593	JL413	652	989-D
476	CGP 47 439	535	5042B	594	5C2E5	653	1A1
477	polyclonal	536	418-D	595	G3-211	654	24G3
478	178.1	537	5021	596	G3-537	655	25C2
479	257-D	538	5025B	597	polyclonal	656	5F3
480	311-11-D	539	5042	598	1795	657	α(566-586)
481	41148D	540	110.3	599	ICR38.1a	658	PC5009
482	391/95-D	541	110.4	600	G3-299	659	polyclonal α577-596
483	Aw	542	110.5	601	G3-42	660	polyclonal
484	Bw	543	58.2	602	G3-508	661	
485	DO142-10	544	polyclonal	603	G3-519	662	
486	Dv	545	KD-247	604	G3-536	663	1F11
487	Fv	546	537-D	605	ICR38.8f	664	1H5
488	Gv	547	5020	606	MO86/C3	665	3D9
489	Hv	548	RC25	607	13H8	666	4B3
490	polyclonal	549	5023A	608	G45-60	667	4D4
491	50.1	550	110.6	609	polyclonal	668	4G2
492		551	polyclonal	610	1662	669	polyclonal
493	BAT123	552	10/36e	611	1663	670	polyclonal
494	838-D	553	10/54	612	1664	671	
495	1006-15D	554	11/85b	613	1697	672	polyclonal
496	782-D	555	polyclonal	614	1794	673	2A2/26
497	908-D	556	0.5β	615	1804	674	50-69
498	1027-15D	557	Cβ1, 0.5β	616	1807	675	9-11
499	F19.26-4	558	C25	617	1808	676	98-43
500	F19.48-3	559	447-52D	618	polyclonal	677	41-1
501	F19.57-11	560	NM-01	619	polyclonal	678	41.4
502	13105100	561	1026	620	CRA1	679	Fab A1
503	M77	562	1034	621	M91	680	Fab A4
504	polyclonal	563	59.1	622	9201	681	Fab M12B
505	SP.BAL114	564	polyclonal	623	1C1	682	Fab M26B
506	SP.SF2:104	565	10E3	624	3F5	683	Fab M8B

Cross Reference Listing of MABs

MABs by order of appearance in tables

684	Fab T2	743	9G11	801	1034	860	AG10H9
685	polyclonal	744	TH-Ab1	802	105-134	861	AH48
686	86	745	polyclonal	803	10E9	862	B4
687	polyclonal	746	polyclonal	804	12.19	863	B5
688	V10-9	747	polyclonal	805	12.9	864	B6
689	polyclonal	748	polyclonal	806	126-50	865	BAT267
690	anti-P1	749	14D9	807	12H2	866	BAT401
691	polyclonal	750	2F5	808	13.10	867	BAT509
692	polyclonal	751	Z13e1	809	1331-D	868	C02-17
693	2F11	752	4E10	810	13H11	869	C02-19
694	246-D	753	Z13	811	13a15	870	C02-34
695	polyclonal	754	B30	812	13a23	871	C02-41
696	9G5A	755	polyclonal	813	13a3	872	C02-53
697	181-D	756	41S-2	814	13a6	873	C02-7
698	240-D	757	C8	815	13a7	874	C18-2
699	F240	758	B31	816	13b53	875	C31
700	D49	759	B33	817	13b61	876	CM51
701	D61	760	1576	818	1492	877	CO11
702	T32	761	1578	819	1B1	878	D02-1
703	T34	762	1579	820	1D10	879	D02-20
704	115.8	763	1583	821	1F7	880	D02-24
705	M-1	764	1899	822	2.5E	881	D02-3
706	M-11	765	1907	823	25G	882	D02-33
707	M-13	766	1908	824	2601	883	D02-34
708	M-2	767	1909	825	2909	884	D02-6
709	M-22	768	41-1	826	2G12	885	D02-7
710	M-24	769	41-2	827	30D	886	D1
711	M-25	770	41-3	828	31710B	887	D12
712	M-28	771	ED6	829	38B5/C9	888	D16
713	M-29	772	LA9 (121-134)	830	39H10/A11	889	D4
714	M-36	773	1575	831	3C9	890	D43
715	M-4	774	88-158/02	832	3D5	891	E047
716	M-6	775	88-158/022	833	3H6	892	E2E
717	polyclonal $\alpha$ 598-609	776	88-158/079	834	4.11C	893	ED10
718	1B8.env	777	polyclonal	835	4.6H	894	EH21
719	polyclonal	778	polyclonal	836	4.8E	895	F1
720	polyclonal	779	B8	837	40D3/C11	896	F223
721	clone 3	780	SAR1	838	412d	897	F285
722	4	781	1577	839	47e	898	F2A3
723	41-6	782	polyclonal	840	49B11/A1	899	F3.9F
724	41-7	783	DZ	841	52G5/B9	900	F424
725	68.1	784	<b>Env</b>	842	55E4/H1	901	F425 B4e8
726	68.11	785		843	56C4/C8	902	F425B4a1
727	75	786		844	570-D	903	F7
728	polyclonal	787		845	57B6/F1	904	Fab A12
729	105-732	788	1.4C	846	57H5/D7	905	Fab A2
730	3D6	789	1.4G	847	5E	906	Fab L9
731	F172-D8	790	1.9E	848	63G4/E2	907	G12
732	D50	791	1.9F	849	65B12/C5	908	G2
733	5-21-3	792	10/540.w	850	694/98D	909	H2
734	120-16	793	1010	851	6D8	910	H8
735	98-6	794	1014	852	6E10	911	HBW4
736	167-7	795	1018	853	7-1054	912	HIVIG
737	ND-15G1	796	1019	854	8.2A	913	IVI-4G6
738	167-D	797	102-135	855	85G11/D8	914	IgA6/30 $\lambda$
739	polyclonal	798	1020	856	87E4/A8	915	IgA6/5k
740	polyclonal	799	1022	857	97B1/E8	916	IgA6/L4
741	polyclonal	800	1025	858	A9	917	K14
742	5B2			859	ADP421 polyclonal	918	KU32

## MABs by order of appearance in tables

## Cross Reference Listing of MABs

919	LA15	978	polyclonal	1037	polyclonal	1096	polyclonal
920	LA21	979	polyclonal	1038	polyclonal	1097	polyclonal
921	M2	980	polyclonal	1039	polyclonal	1098	polyclonal
922	M25	981	polyclonal	1040	polyclonal	1099	polyclonal
923	MAG 6B	982	polyclonal	1041	polyclonal	1100	polyclonal
924	MO28	983	polyclonal	1042	polyclonal	1101	101-342
925	MO30	984	polyclonal	1043	polyclonal	1102	101-451
926	MO43	985	polyclonal	1044	polyclonal	1103	120-1
927	N2-4	986	polyclonal	1045	polyclonal	1104	T26
928	N70-2.3a	987	polyclonal	1046	polyclonal	1105	D33
929	P3C8	988	polyclonal	1047	polyclonal	1106	polyclonal
930	P3E1	989	polyclonal	1048	polyclonal	1107	212A
931	P43110	990	polyclonal	1049	polyclonal	1108	522-149
932	P5-3	991	polyclonal	1050	polyclonal	1109	CA1
933	PA-1	992	polyclonal	1051	polyclonal	1110	L19
934	Sb1	993	polyclonal	1052	polyclonal	1111	M90
935	T15G1	994	polyclonal	1053	polyclonal	1112	MAG 104
936	T20	995	polyclonal	1054	polyclonal	1113	MAG 45
937	T27	996	polyclonal	1055	polyclonal	1114	MAG 95
938	T3	997	polyclonal	1056	polyclonal	1115	MAG 97
939	T30	998	polyclonal	1057	polyclonal	1116	P35
940	T4	999	polyclonal	1058	polyclonal	1117	T9
941	m14	1000	polyclonal	1059	polyclonal	1118	p7
942	m16	1001	polyclonal	1060	polyclonal	1119	L100
943	m18	1002	polyclonal	1061	polyclonal	1120	2/11c
944	m22	1003	polyclonal	1062	polyclonal	1121	A32
945	m24	1004	polyclonal	1063	polyclonal	1122	C11
946	m46	1005	polyclonal	1064	polyclonal	1123	L81
947	m9	1006	polyclonal	1065	polyclonal	1124	polyclonal
948	multiple Fabs	1007	polyclonal	1066	polyclonal	1125	1024
949	multiple MABs	1008	polyclonal	1067	polyclonal	1126	4KG5
950	multiple MABs	1009	polyclonal	1068	polyclonal	1127	23A
951	multiple MABs	1010	polyclonal	1069	polyclonal	1128	D7324
952	polyclonal	1011	polyclonal	1070	polyclonal	1129	10/46c
953	polyclonal	1012	polyclonal	1071	polyclonal	1130	1008-D
954	polyclonal	1013	polyclonal	1072	polyclonal	1131	1027-30-D
955	polyclonal	1014	polyclonal	1073	polyclonal	1132	1125H
956	polyclonal	1015	polyclonal	1074	polyclonal	1133	1125H
957	polyclonal	1016	polyclonal	1075	polyclonal	1134	120-1B1
958	polyclonal	1017	polyclonal	1076	polyclonal	1135	1202-D
959	polyclonal	1018	polyclonal	1077	polyclonal	1136	1331E
960	polyclonal	1019	polyclonal	1078	polyclonal	1137	1570
961	polyclonal	1020	polyclonal	1079	polyclonal	1138	1595
962	polyclonal	1021	polyclonal	1080	polyclonal	1139	1599
963	polyclonal	1022	polyclonal	1081	polyclonal	1140	15e
964	polyclonal	1023	polyclonal	1082	polyclonal	1141	21h
965	polyclonal	1024	polyclonal	1083	polyclonal	1142	28A11/B1
966	polyclonal	1025	polyclonal	1084	polyclonal	1143	2G6
967	polyclonal	1026	polyclonal	1085	polyclonal	1144	35F3/E2
968	polyclonal	1027	polyclonal	1086	polyclonal	1145	38G3/A9
969	polyclonal	1028	polyclonal	1087	polyclonal	1146	428
970	polyclonal	1029	polyclonal	1088	polyclonal	1147	448-D
971	polyclonal	1030	polyclonal	1089	polyclonal	1148	46D2/D5
972	polyclonal	1031	polyclonal	1090	polyclonal	1149	48-16
973	polyclonal	1032	polyclonal	1091	polyclonal	1150	50-61A
974	polyclonal	1033	polyclonal	1092	polyclonal	1151	5145A
975	polyclonal	1034	polyclonal	1093	polyclonal	1152	558-D
976	polyclonal	1035	polyclonal	1094	polyclonal	1153	559/64-D
977	polyclonal	1036	polyclonal	1095	polyclonal	1154	55D5/F9

Cross Reference Listing of MABs

MABs by order of appearance in tables

1155	588-D	1214	TH9	1273	2442	1332	Fab S6
1156	654-D	1215	anti-CD4BS summary	1274	2456	1333	Fab S8
1157	67G6/C4	1216	b11	1275	2483	1334	Fab S9
1158	729-D	1217	b13	1276	2497	1335	Fab T3
1159	830D	1218	b14	1277	2557	1336	Md-1
1160	9CL	1219	b3	1278	2558	1337	Fab A9
1161	BM12	1220	b6	1279	2580	1338	Fab G15
1162	D20	1221	polyclonal	1280	391/95-D	1339	Fab G5
1163	D21	1222		1281	39F	1340	Fab L1
1164	D24	1223	17b	1282	4148d	1341	Fab L11
1165	D25	1224	21c	1283	55/68b	1342	Fab L2
1166	D28	1225	23e	1284	5G11	1343	1281
1167	D35	1226	48d	1285	6.1	1344	Chessie 8
1168	D39	1227	49e	1286	6.7	1345	8F102
1169	D42	1228	Fbb21	1287	8.27.3	1346	CG-10
1170	D52	1229	Fbb21	1288	8E11/A8	1347	CG-25
1171	D53	1230	X5	1289	9305	1348	CG-4
1172	D60	1231	8F101	1290	A1g8	1349	CG-76
1173	DA48	1232	T22	1291	AG1121	1350	CG-9
1174	DO8i	1233	2A2	1292	Ag1211	1351	105-518
1175	F105	1234	AC4	1293	B4a1	1352	31A1
1176	F91	1235	AD3	1294	B4e8	1353	39A64
1177	FG39	1236	AD3	1295	D27	1354	39B86
1178	Fbb14	1237	ID6	1296	D47	1355	9303
1179	GP13	1238	ID6	1297	D56	1356	NC-1
1180	GP44	1239	11/68b	1298	F5.5		<b>Nef</b>
1181	GP68	1240	62c	1299	G3-1472	1357	4H4
1182	HF1.7	1241	CRA-6	1300	K24	1358	polyclonal
1183	HT5	1242	L15	1301	TH1	1359	13/042
1184	HT6	1243	T52	1302	anti-gp120/V3	1360	13/035
1185	HT7	1244	T54	1303	polyclonal	1361	A6
1186	ICR 39.13g	1245	polyclonal	1304	polyclonal	1362	AM5C6
1187	ICR 39.3b	1246	1088	1305	polyclonal	1363	AM5C6
1188	Ia3	1247	110-B	1306	polyclonal	1364	A7
1189	Ia7	1248	1357	1307	polyclonal	1365	25/03
1190	IgG1b12	1249	1361	1308	polyclonal	1366	26/76
1191	IgGCD4	1250	1393A	1309	polyclonal	1367	3F2
1192	L28	1251	2158	1310	polyclonal	1368	3D12
1193	L33	1252	66a	1311	polyclonal	1369	polyclonal
1194	L41	1253	66c	1312	11/75a/21/41	1370	polyclonal
1195	L42	1254	684-238	1313	41.1	1371	3G12
1196	L52	1255	830A	1314	55/45a/11	1372	13/058
1197	L72	1256	CRA-3	1315	1108	1373	26/028
1198	M12	1257	CRA-4	1316	polyclonal	1374	polyclonal
1199	M13	1258	L17	1317	polyclonal	1375	2E3
1200	M6	1259	SC258	1318	polyclonal	1376	polyclonal
1201	MAG 116	1260	L25	1319	1367	1377	F14.11
1202	MAG 12B	1261	L39	1320	7B2	1378	31/03
1203	MAG 29B	1262	L40	1321	126-6	1379	polyclonal
1204	MAG 3B	1263	L78	1322	1342	1380	polyclonal
1205	MAG 55	1264		1323	1379	1381	F4
1206	MAG 72	1265	10D8	1324	2.2B	1382	F2
1207	MAG 86	1266	10F6	1325	Fab D11	1383	polyclonal
1208	MAG 96	1267	110.J	1326	Fab D5	1384	polyclonal
1209	MTW61D	1268	11G5	1327	Fab G1	1385	polyclonal
1210	S1-1	1269	2182	1328	Fab M10	1386	F3
1211	T13	1270	2191	1329	Fab M12	1387	F8
1212	T49	1271	2219	1330	Fab M15	1388	polyclonal
1213	T56	1272	2412	1331	Fab S10	1389	F1



- 1390 2F2
- 1391 E9
- 1392 3E6
- 1393 E5
- 1394 2A3
- 1395 2E4
- 1396 2H12
- 1397 3A2
- 1398 NF1A1
- 1399 polyclonal
- 1400 E7
- 1401 AE6
- 1402 AG11
- 1403 EH1
- 1404 3B4B
- 1405 3H3E
- 1406 6.1
- 1407 NF2B2
- 1408 NF3A3
- 1409 NF8B4
- 1410 polyclonal
- 1411 AE6
- HIV-1**
- 1412
- 1413
- 1414
- 1415 13b18
- 1416 13b23
- 1417 LA28
- 1418 LF17
- 1419 polyclonal
- 1420 polyclonal
- 1421 polyclonal
- 1422 polyclonal
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- 1445 polyclonal
- 1446 polyclonal
- 1447 polyclonal

1448 polyclonal



## IV-C

# HIV Antibodies Tables

All HIV MAbs and polyclonal Abs that bind to linear epitopes 30 amino acids or less in length are arranged by protein position. The table entries are sorted in a nested way—first by protein, then by HXB2 start location, then by antibody type, and finally by antibody name. Abs that bind to conformational epitopes or with unknown epitopes are listed at the end of each protein section.

### IV-C-1 Gag p17 Antibodies

#### No. 1

**MAb ID** L14.17

**HXB2 Location** p17 (11–25)

**Author Location** p17 (11–25 BRU)

**Epitope** GELDRWEKIRLRPGG

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* viral lysate *Strain:* B clade BRU *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG)

**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Tatsumi *et al.* 1990

#### No. 2

**MAb ID** polyclonal

**HXB2 Location** p17 (11–25)

**Author Location** p17 (11–25 LAI)

**Epitope** GELDRWEKIRLRPGG

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* Gag, p17 Gag, p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse

**References** Truong *et al.* 1997

- An ELISA assay was used to study a panel of Gag peptides – mature p24 CA epitopes mapped to residues 176–192, 201–218, 233–253, 285–304, and were recognized by antibodies elicited by rp24CA – one p17MA epitope, residues 11–25, and one p24CA epitope, residues 176–192, were recognized by antibodies raised against anti-p55 virus-like particles, suggesting a different antigenic properties for p24CA and p17MA antibodies depending on whether they are produced against the mature soluble protein or the immature assembled form of the gag proteins. Truong *et al.* [1997]

#### No. 3

**MAb ID** 32/5.8.42

**HXB2 Location** p17 (12–19)

**Author Location** p17 (12–19 IIIB)

**Epitope** ELDRWEKI+ALDKIE

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* viral lysate

**Species (Isotype)** mouse (IgG)

**References** Papsidero *et al.* 1989

- 32/5.8.42: Binds to two discontinuous regions, positions 12–19 and 100–105, peptides ELDRWEKI and ALDKIE – inhibited infectivity of cell free virus. Papsidero *et al.* [1989]

#### No. 4

**MAb ID** 32/5.8.42

**HXB2 Location** p17 (12–19)

**Author Location** p17 (IIIB)

**Epitope** ELDRWEKI+ALDKIE

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* viral lysate *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG)

**References** Papsidero *et al.* 1989

- 32/5.8.42: Inhibited infectivity of cell free virus – bound to two peptides, ELDRWEKI and ALDKIE, at positions 12–19 + 100–105. Papsidero *et al.* [1989]

#### No. 5

**MAb ID** HyHIV-1

**HXB2 Location** p17 (12–29)

**Author Location** p17 (12–29 JMH1)

**Epitope** ELDKWEKIRLRPGGKTLTLY

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* p17 Gag

**Species (Isotype)** mouse (IgG1)

**References** Ota & Ueda 1998; Liu *et al.* 1995

- HyHIV-1: This paper compares the results of affinity constant ( $K_a$ ) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

#### No. 6

**MAb ID** HyHIV-2

**HXB2 Location** p17 (12–29)

**Author Location** p17 (12–29 JMH1)

**Epitope** ELDKWEKIRLRPGGKTLTLY

**Neutralizing** no**Immunogen** vaccine*Vector/Type:* protein *HIV component:* p17  
Gag**Species (Isotype)** mouse (IgG1)**References** Ota & Ueda 1998; Liu *et al.* 1995

- HyHIV-2: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 7

**MAb ID** HyHIV-3**HXB2 Location** p17 (12–29)**Author Location** p17 (12–29 JMH1)**Epitope** ELDKWEKIRLRPGGKTLTY**Neutralizing** no**Immunogen** vaccine*Vector/Type:* protein *HIV component:* p17  
Gag**Species (Isotype)** mouse (IgG1)**References** Ota & Ueda 1998; Liu *et al.* 1995

- HyHIV-3: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 8

**MAb ID** HyHIV-4**HXB2 Location** p17 (12–29)**Author Location** p17 (12–29 JMH1)**Epitope** ELDKWEKIRLRPGGKTLTY?**Neutralizing** no**Immunogen** vaccine*Vector/Type:* protein *HIV component:* p17  
Gag**Species (Isotype)** mouse (IgG1)**References** Ota & Ueda 1998; Ota *et al.* 1998; Liu *et al.* 1995

- HyHIV-4: epitope uncertain, based on the best estimate from JMH1 sequence– Ka is  $1.8 \times 10^7$  M<sup>-1</sup> for rec p17 – stains the surface of infected cells indicating the antigen is exposed at the cell surface. Ota *et al.* [1998]
- HyHIV-4: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 9

**MAb ID** HyHIV-5**HXB2 Location** p17 (12–29)**Author Location** p17 (12–29 JMH1)**Epitope** ELDKWEKIRLRPGGKTLTY**Neutralizing** no**Immunogen** vaccine*Vector/Type:* protein *HIV component:* p17  
Gag**Species (Isotype)** mouse (IgG1)**References** Ota & Ueda 1998; Liu *et al.* 1995

- HyHIV-5: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 10

**MAb ID** HyHIV-6**HXB2 Location** p17 (12–29)**Author Location** p17 (12–29 JMH1)**Epitope** ELDKWEKIRLRPGGKTLTY**Neutralizing** no**Immunogen** vaccine*Vector/Type:* protein *HIV component:* p17  
Gag**Species (Isotype)** mouse (IgG1)**References** Ota & Ueda 1998; Liu *et al.* 1995

- HyHIV-6: This paper compares the results of affinity constant (Ka) measurements of anti-p17 MAbs using double Ab methods versus the faster, isotope-free BIAcore system, and results were found to be similar for HyHIV-(1-6) – six MAbs all bind to the first alpha helix of p17, a functional domain for both membrane binding and nuclear localization. Ota & Ueda [1998]

No. 11

**MAb ID** 32/1.24.89**HXB2 Location** p17 (17–22)**Author Location** p17 (17–22 IIIB)**Epitope** EKIRLR**Neutralizing** L**Immunogen** vaccine*Vector/Type:* viral lysate**Species (Isotype)** mouse (IgG)**References** Papsidero *et al.* 1989

- 32/1.24.89: Inhibited infectivity of cell free virus. Papsidero *et al.* [1989]

No. 12

**MAb ID** 3B10**HXB2 Location** p17 (19–38)**Author Location** p17 (19–38 SIVmac)**Epitope** IRLPGGKKKYM LKHVVWAA**Neutralizing** no**Immunogen** vaccine*Vector/Type:* inactivated *HIV Strain:*  
B clade AGM TYO-7 *HIV component:*  
HIV-1**Species (Isotype)** mouse (IgG1)**References** Otteken *et al.* 1992

- 3B10: Recognized an epitope present on HIV-2/SIVmac (MAC251/32H), SIVagm, HIV-1, and SIVmnd, demonstrating that the matrix protein of all nine HIV and SIV isolates tested in this study expresses at least one conserved immunogenic epitope recognized serologically. Otteken *et al.* [1992]

No. 13

**MAb ID** 3E11

**HXB2 Location** p17 (19–38)

**Author Location** p17 (19–38 SIVmac)

**Epitope** IRLPGGKKKYMLKHVVAA

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* B clade AGM TYO-7 *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1)

**References** Nilsen *et al.* 1996; Otteken *et al.* 1992

- 3E11: There is another MAb with this ID that recognizes integrase. Nilsen *et al.* [1996]
- 3E11: Recognized an epitope present on HIV-2/SIVmac (MAC251/32H), SIVagm, HIV-1, and SIVmnd, demonstrating that the matrix protein of all nine HIV and SIV isolates tested in this study expresses at least one highly conserved immunogenic epitope. Otteken *et al.* [1992]

No. 14

**MAb ID** polyclonal

**HXB2 Location** p17 (25–34)

**Author Location** Gag

**Epitope** GKTHYMINPL

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* Env, Gag, Nef, Pol

**Species (Isotype)** rabbit

**References** Li *et al.* 2005

**Keywords** mimics

- In early HIV-1 infection, patients develop autoimmune thrombocytopenia, with Ab directed against beta3 integrin, GPIIIa49-66. Panning with a 7-mer phage display library using rabbit anti-GPIIIa49-66 (CAPESIEFPVSEARVLED), the immunodominant epitope of the identified potential molecular mimicry epitopes with HIV-1 Env (sklFDeGLFn, elfnk-TIIFP), Pol (geAPEFPskq), Gag (gktHyMINPI) and Nef (qeeeeVgFPVt, qeeeeVgFPVt, edeGigFPVr, fklVPVSEae, ssnTPTTNa) proteins. Pools of these peptides elicited Ab in rabbits that induce platelet oxidation in vitro and thrombocytopenia in vivo upon passive transfer. Nef (qeeeeVgFPVt), Gag (gktHyMINPI), and Nef (fklVPVSEae) all overlap with known HIV-1 epitopes. Li *et al.* [2005] (**mimics**)

No. 15

**MAb ID** 8H10

**HXB2 Location** p17 (30–52)

**Author Location** p17 (30–52 JMH1)

**Epitope** KLKHIVWASRELERFAVNPGLLE

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade JMH-1 *HIV component:* p17 Gag *Adjuvant:* BSA

**Species (Isotype)** mouse (IgM)

**References** Ota & Ueda 1999; Ota *et al.* 1999

- 8H10: The p17 MAb also can bind to the V3 loop. Ota *et al.* [1999]
- 8H10: Inhibits viral replication of the HIV-1 infected MT-4 cells by decreasing p17 DNA levels in the infected cells, and the effect of growing the 8H10 hybridoma in co-culture with HIV-1 infected MT-4 cells was studied. Ota & Ueda [1999]

No. 16

**MAb ID** HyHIV-21

**HXB2 Location** p17 (30–52)

**Author Location** p17 (30–52 JMH1)

**Epitope** KLKHIIWASRELERFAVNPGLLE

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* p17 Gag

**Species (Isotype)** mouse (IgG2a)

**References** Ota *et al.* 1998; Liu *et al.* 1995

- HyHIV-21: epitope uncertain, based on the best estimate from JMH1 sequence – Ka is  $3.6 \times 10^6$  M<sup>-1</sup> for rec p17 – stains the surface of infected cells indicating the antigen is exposed at the cell surface –inhibited growth of HIV-1 JMH1 in MT-4 cells when added 24 hours after the initial culture. Ota *et al.* [1998]

No. 17

**MAb ID** B4f8

**HXB2 Location** p17 (51–65)

**Author Location** p17 (51–65)

**Epitope** LETSEGCRQILGQLQ

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* HIV infected-cell lysate *Strain:* B clade IIIB *HIV component:* HIV-1

**Species (Isotype)** rat (IgG2a)

**References** Shang *et al.* 1991

- -B4f8: Did not bind live infected cells, only cells that had been made permeable with acetone. Shang *et al.* [1991]

No. 18

**MAb ID** HyHIV-22

**HXB2 Location** p17 (52–83)

**Author Location** p17 (53–87 JMH1)

**Epitope** ETSEGCRQILGQRQPSLQGTGSEELRSYNTIH

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* p17 Gag

**Species (Isotype)** mouse (IgG1)

**References** Ota *et al.* 1998; Liu *et al.* 1995

- HyHIV-22: epitope uncertain, based on the best estimate from JMH1 sequence – stains the surface of infected cells indicating the antigen is exposed at the cell surface – Ka is  $2.3 \times 10^5$  M<sup>-1</sup> for rec p17. Ota *et al.* [1998]

**No. 19**  
**MAb ID** 12H-D3b3  
**HXB2 Location** p17 (62–78)  
**Author Location** p17 (62–78)  
**Epitope** GQLQPSLQTGSEELRSL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* HIV infected-cell lysate  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** rat (IgG2a)  
**References** Shang *et al.* 1991  
 • 12H-D3b3: Did not bind live infected cells, only cells that had been made permeable with acetone. Shang *et al.* [1991]

**No. 20**  
**MAb ID** 12G-A8g2  
**HXB2 Location** p17 (86–115)  
**Author Location** p17 (86–115)  
**Epitope** YCVHQRIEIKDTKEALDKIEEEQNKSKKKA  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* HIV infected-cell lysate  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** rat (IgG2a)  
**References** Maksiutov *et al.* 2002; Shang *et al.* 1991  
 • 12G-A8g2: This epitope is similar to a fragment of the human protein CD40 ligand TNF-related activation protein (T-cell antigen GP39) (CD154), LDKIEDERN, as well as to a fragment of Lens-epithelium-derived growth factor, DIITEEDKSKKKKGQ. Maksiutov *et al.* [2002]  
 • 12G-A8g2: Bound to 30-mer, but not to internal peptides – did not bind live infected cells – antigenic domain known as HPG30. Shang *et al.* [1991]

**No. 21**  
**MAb ID** 12G-D7h11  
**HXB2 Location** p17 (86–115)  
**Author Location** p17 (86–115)  
**Epitope** YCVHQRIEIKDTKEALDKIEEEQNKSKKKA  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* HIV infected-cell lysate  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** rat (IgG2a)  
**References** Maksiutov *et al.* 2002; Shang *et al.* 1991  
 • 12G-D7h11: This epitope is similar to a fragment of the human protein CD40 ligand TNF-related activation protein (T-cell antigen GP39) (CD154), LDKIEDERN, as well as to a fragment of Lens-epithelium-derived growth factor, DIITEEDKSKKKKGQ. Maksiutov *et al.* [2002]  
 • 12G-D7h11: Bound to 30-mer, but not to internal peptides – did not bind live infected cells – antigenic domain known as HPG30. Shang *et al.* [1991]

**No. 22**  
**MAb ID** 12G-H1c7  
**HXB2 Location** p17 (86–115)

**Author Location** p17 (86–115)  
**Epitope** YCVHQRIEIKDTKEALDKIEEEQNKSKKKA  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* HIV infected-cell lysate  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** rat (IgG)  
**References** Maksiutov *et al.* 2002; Shang *et al.* 1991  
 • 12G-H1c7: This epitope is similar to a fragment of the human protein CD40 ligand TNF-related activation protein (T-cell antigen GP39) (CD154), LDKIEDERN, as well as to a fragment of Lens-epithelium-derived growth factor, DIITEEDKSKKKKGQ. Maksiutov *et al.* [2002]  
 • 12G-H1c7: Bound to 30-mer, but not to internal peptides – did not bind live infected cells – antigenic domain known as HPG30. Shang *et al.* [1991]

**No. 23**  
**MAb ID** 12I-D12g2  
**HXB2 Location** p17 (86–115)  
**Author Location** p17 (86–115)  
**Epitope** YCVHQRIEIKDTKEALDKIEEEQNKSKKKA  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* HIV infected-cell lysate  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** rat (IgG2a)  
**References** Maksiutov *et al.* 2002; Shang *et al.* 1991  
 • 12I-D12g2: This epitope is similar to a fragment of the human protein CD40 ligand TNF-related activation protein (T-cell antigen GP39) (CD154), LDKIEDERN, as well as to a fragment of Lens-epithelium-derived growth factor, DIITEEDKSKKKKGQ. Maksiutov *et al.* [2002]  
 • 12I-D12g2: Bound to 30-mer, but not to internal peptides – did not bind live infected cells – antigenic domain known as HPG30. Shang *et al.* [1991]

**No. 24**  
**MAb ID** polyclonal  
**HXB2 Location** p17 (86–115)  
**Author Location** p17 (86–115)  
**Epitope** YSVHQRIDVKDTKEALEKIEEEQNKSKKKA  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* p17 Gag *Adjuvant:* Cholera toxin (CT)  
**Species (Isotype)** mouse (IgA)  
**References** Bukawa *et al.* 1995  
 • Polyclonal secretory IgA antibody raised by oral mucosal immunization is able to neutralize IIIB, SF2, and MN – HIV-1 neutralization may be due to the V3, CD4 or HPG30 component of the multicomponent peptide immunogen. Bukawa *et al.* [1995]

**No. 25**  
**MAb ID** HyHIV-15  
**HXB2 Location** p17 (87–115)  
**Author Location** p17 (87–115 JMH1)

**Epitope** SVHQRIDVKDTKEALEKIEEEQNKSKKKA?  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p17  
 Gag  
**Species (Isotype)** mouse (IgG1)  
**References** Ota *et al.* 1998; Liu *et al.* 1995  
 • HyHIV-15: epitope uncertain, based on the best estimate from JMHI sequence – Ka is  $1.4 \times 10^7$  M<sup>-1</sup> for rec p17 – stains the surface of infected cells indicating the antigen is exposed at the cell surface – inhibited growth of HIV-1 JMHI in MT-4 cells when added 24 hours after the initial culture. Ota *et al.* [1998]

**No. 26**  
**MAb ID** 11H9  
**HXB2 Location** p17 (101–115)  
**Author Location** p17 (101–115 SF2)  
**Epitope** LEKIEEEQNKSKKKA?  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**Research Contact** R. B. Ferns and R. S. Tedder  
**References** Maksutov *et al.* 2002; Ferns *et al.* 1989; Ferns *et al.* 1987  
 • 11H9: UK Medical Research Council AIDS reagent: ARP344.  
 • 11H9: This epitope is similar to a fragment of Lens-epithelium-derived growth factor, DIITEEDKSKKKGQ. Maksutov *et al.* [2002]  
 • 11H9: Reactive against p18 and p55. Ferns *et al.* [1987]

**No. 27**  
**MAb ID** 3-H-7 (3H7)  
**HXB2 Location** p17 (113–122)  
**Author Location** p17 (113–122 BH10)  
**Epitope** KKAQQAADT  
**Neutralizing** L  
**Immunogen** vaccine  
*Strain:* B clade IIIB  
**Species (Isotype)** mouse (IgG)  
**References** Levin *et al.* 1997; Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Niedrig *et al.* 1989  
 • 3-H-7: Called 3H7 – using a bicistronic vector, an intracellular Fab intrabody, 3H7, can inhibit HIV-1 infection when expressed in the cytoplasm of dividing CD4+ T cells – HXBI-IIB and SI primary isolate virions from 3H7 expressing cells were far less infectious – 3H7 intrabody acts both at the stage of nuclear import and virus particle assembly. Levin *et al.* [1997]  
 • 3-H-7: No cross-reactivity with HIV-2 ROD or SIV MAC by immunoblot. Niedrig *et al.* [1989]

**No. 28**  
**MAb ID** C5126  
**HXB2 Location** p17 (113–122)  
**Author Location** p17 (113–122 HXB2)

**Epitope** KKAQQAADT  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* viral lysate *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1κ)  
**References** Hinkula *et al.* 1990  
 • C5126: Defined epitope by peptide blocking of binding to native protein – WB reactive with p53 and p17. Hinkula *et al.* [1990]

**No. 29**  
**MAb ID** 1D9  
**HXB2 Location** p17 (119–132)  
**Author Location** p17 (121–134 SF2)  
**Epitope** AAGTGNSSQVSQNY  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG2a)  
**Research Contact** R. B. Ferns and R. S. Tedder  
**References** Ferns *et al.* 1989; Ferns *et al.* 1987  
 • 1D9: UK Medical Research Council AIDS reagent: ARP316.  
 • 1D9: Reactive against p18, but not p55. Ferns *et al.* [1987]

**No. 30**  
**MAb ID** 4C9  
**HXB2 Location** p17 (119–132)  
**Author Location** p18 (121–134 SF2)  
**Epitope** AAGTGNSSQVSQNY  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG2a)  
**Research Contact** R. B. Ferns and R. S. Tedder  
**References** Ferns *et al.* 1989; Ferns *et al.* 1987  
 • 4C9: UK Medical Research Council AIDS reagent: ARP342.  
 • 4C9: Reactive against p18, but not p55. Ferns *et al.* [1987]

**No. 31**  
**MAb ID** 4H2B1  
**HXB2 Location** p17 (119–132)  
**Author Location** p17 (121–134 SF2)  
**Epitope** AAGTGNSSQVSQNY  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** mouse (IgG1)  
**Research Contact** R. B. Ferns and R. S. Tedder  
**References** Ferns *et al.* 1989; Ferns *et al.* 1987  
 • 4H2B1: UK Medical Research Council AIDS reagent: ARP315.  
 • 4H2B1: Reactive against p18 and p55 of multiple isolates. Ferns *et al.* [1987]

**No. 32**  
**MAb ID** 9G5  
**HXB2 Location** p17 (119–132)

**Author Location** p17 (121–134 SF2)  
**Epitope** AAGTGNSSQVSQNY  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgM)  
**Research Contact** R. B. Ferns and R. S. Tedder  
**References** Ferns *et al.* 1989; Ferns *et al.* 1987  
 • 9G5: UK Medical Research Council AIDS reagent: ARP343.  
 • 9G5: Reactive against p18, but not p55. Ferns *et al.* [1987]

**No.** 33

**MAb ID** 15-21

**HXB2 Location** p17 (121–132)

**Author Location** p17 (121–132 BRU)

**Epitope** DTGHSSQVSQNY

**Neutralizing** no

**Immunogen** vaccine

*Strain:* B clade BRU

**Species (Isotype)** mouse (IgG)

**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

**No.** 34

**MAb ID** 31-11

**HXB2 Location** p17 (121–132)

**Author Location** p17 (121–132 BRU)

**Epitope** DTGHSSQVSQNY

**Neutralizing** no

**Immunogen** vaccine

*Strain:* B clade BRU

**Species (Isotype)** mouse (IgG)

**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

**No.** 35

**MAb ID** sc-FV p17

**HXB2 Location** p17 (121–132)

**Author Location** p17 (121–132 BRU)

**Epitope** DTGHSSQVSQNY

**Neutralizing** L

**Immunogen** vaccine

*Strain:* B clade BRU

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** C-term

**Research Contact** Paul Zhou, NIH, Bethesda, MD, USA

**References** Tewari *et al.* 1998; Robert-Hebmann *et al.* 1992a

- A single chain Ab (sc-FV) was made from an anti-p17 MAb, and intracellular binding of sc-FV resulted in inhibition of viral replication that was more pronounced when the sc-FV was expressed in the cytoplasm instead of the nucleus. Tewari *et al.* [1998]

## IV-C-2 Gag p17-p24 Antibodies

**No.** 36

**MAb ID** 3A6

**HXB2 Location** p17-p24 (122–17)

**Author Location** p24 (122–149 BH10)

**Epitope** TGHSSQVSQNYPIVQNIQGMVHQAIISP

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**References** Buchacher *et al.* 1994; Buchacher *et al.* 1992

- 3A6: The reactive peptide spans the p17/p24 border of gag. Buchacher *et al.* [1994]
- 3A6: Human MAbs against HIV generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994]

## IV-C-3 Gag p24 Antibodies

**No.** 37

**MAb ID** 111/182

**HXB2 Location** p24 (1–20)

**Author Location** p24 (134–153 IIIB)

**Epitope** PIVQNIQGMVHQAIISPRTL

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag

**Species (Isotype)** mouse (IgG1)

**References** Niedrig *et al.* 1991

- 111/182: Test specific evidence of cross-reactivity between HIV-1, HIV-2 and SIV MAC. Niedrig *et al.* [1991]

**No.** 38

**MAb ID** 112/021

**HXB2 Location** p24 (1–20)

**Author Location** p24 (134–153 IIIB)

**Epitope** PIVQNIQGMVHQAIISPRTL

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag

**Species (Isotype)** mouse (IgG1)

**References** Niedrig *et al.* 1991

- 112/021: Test specific evidence of cross-reactivity between HIV-1, HIV-2 and SIV MAC. Niedrig *et al.* [1991]

**No.** 39

**MAb ID** 112/047

**HXB2 Location** p24 (1–20)

**Author Location** p24 (134–153 IIIB)

**Epitope** PIVQNIQGMVHQAIISPRTL

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag



**Species (Isotype)** mouse (IgG1)

**References** Niedrig *et al.* 1991

- 112/047: Test specific evidence of cross-reactivity between HIV-1, HIV-2 and SIV MAC. Niedrig *et al.* [1991]

**No.** 40

**MAb ID** ID8F6

**HXB2 Location** p24 (11–25)

**Author Location** p24 (143–157 BRU)

**Epitope** VHQAISPRTLNAWVK

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1)

**Research Contact** R. B. Ferns and R. S. Tedder

**References** Ferns *et al.* 1989; Ferns *et al.* 1987

- ID8F6: UK Medical Research Council AIDS reagent: ARP348.
- ID8F6: Reacted with both p55 and p24 – showed less than 75% homologous inhibition. Ferns *et al.* [1987]

**No.** 41

**MAb ID** F5-2

**HXB2 Location** p24 (14–23)

**Author Location** p24 (14–23 HXB2)

**Epitope** AISPRTLNAW

**Subtype** B

**Neutralizing** no

**Immunogen**

**Species (Isotype)** mouse

**References** Kusk *et al.* 1992; Kusk *et al.* 1988

- F5-2: In HIV-1 + individuals, antibody to AISPRTLNAW is associated with CD4 T-cell decline. Kusk *et al.* [1988, 1992]

**No.** 42

**MAb ID** CB-13/5 (CB-mab-p24/13-15)

**HXB2 Location** p24 (21–25)

**Author Location** p24 (152–156)

**Epitope** NAWVK

**Neutralizing** no

**Immunogen**

**Species (Isotype)** mouse (IgG1κ)

**References** Glaser & Hausdorf 1996; Kuttner *et al.* 1992; Franke *et al.* 1992; Grunow *et al.* 1990

- CB-13/5 database comment: It is not clear whether the MAbs CD-13/5 and CB-mab-p24/13-15 are the same, but from the shared references in the primary articles they seem to be.
- CB-13/5: Epitope described as VHQAISPRTLNAWVK – binding not affected by bound MAb CB-4/1. Glaser & Hausdorf [1996]
- CB-13/5: Inhibits spread of HIV-1 in cell cultures. Franke *et al.* [1992]
- CB-13/5: Called CB-mab-p24/13-15 – the VDJ H and VJ L regions of CB-mab-p24/13-15 were sequenced. Kuttner *et al.* [1992]

**No.** 43

**MAb ID** polyclonal

**HXB2 Location** p24 (44–60)

**Author Location** p24 (176–192 LAI)

**Epitope** SEGATPQDLNTMLNTVG

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* Gag, p17 Gag, p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse (IgG)

**References** Truong *et al.* 1997

- An ELISA assay was used to study a panel of Gag peptides – mature p24 CA epitopes mapped to residues 176-192, 201-218, 233-253, 285-304, and were recognized by antibodies elicited by rp24CA – one p17MA epitope, residues 11-25, and one p24CA epitope, residues 176-192, were recognized by antibodies raised against anti-p55 virus-like particles, suggesting a different antigenic properties for p24CA and p17MA antibodies depending on whether they are produced against the mature soluble protein or the immature assembled form of the gag proteins. Truong *et al.* [1997]

**No.** 44

**MAb ID** 3D3

**HXB2 Location** p24 (45–50)

**Author Location** p24 (177–182 LAI)

**Epitope** EGATPQ

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG2b)

**Research Contact** R. B. Ferns and R. S. Tedder

**References** Ferns *et al.* 1989; Ferns *et al.* 1987

- 3D3: UK Medical Research Council AIDS reagent: ARP314.
- 3D3: Most broadly reactive of all the antibodies in this study. Ferns *et al.* [1987]

**No.** 45

**MAb ID** CD-4/1 (CB-4/1/1/F6)

**HXB2 Location** p24 (46–56)

**Author Location** p24 (182–197)

**Epitope** GATPQDLNTML

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* beta-galactosidase fusion protein *HIV component:* p24 Gag

**Species (Isotype)** mouse (IgG2ak)

**References** Ehrhard *et al.* 1996; Glaser & Hausdorf 1996; Hohne *et al.* 1993; Franke *et al.* 1992; Grunow *et al.* 1990

- CD-4/1: Modification of p24 lysine residues by maleic anhydride increased the affinity of CD-4/1, presumably due to conformational changes exposing a cryptic epitope. Ehrhard *et al.* [1996]
- CD-4/1: Unusual p24-MAb binding kinetics, with biphasic association – probably due to conformational changes in p24, not to p24 dimerization. Glaser & Hausdorf [1996]

- CD-4/1: Affinity of CB-4/1 to native p24 is lower than to peptide or denatured p24 – proposed that the peptide binds in a loop conformation. Hohne *et al.* [1993]
- CD-4/1: Inhibits spread of HIV-1 in cell cultures. Franke *et al.* [1992]

No. 46

**MAb ID** 15F8C7**HXB2 Location** p24 (47–56)**Author Location** p24 (183–197)**Epitope** ATPQDLNTML**Neutralizing** no**Immunogen** vaccine*Vector/Type:* purified HIV-1**Species (Isotype)** mouse (IgG1)**References** Janvier *et al.* 1992; Janvier *et al.* 1990

- 15F8C7: Mapped to aa209-217 through Pepsan method – cross-reacts with HIV-2 Janvier *et al.* [1990] – maps to aa203-217 through EIA pentadecapeptide Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

No. 47

**MAb ID** 111/052**HXB2 Location** p24 (51–60)**Author Location** p24 (183–192 IIIB)**Epitope** DLNTMLNTVG**Neutralizing** no**Immunogen** vaccine*Vector/Type:* beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag**Species (Isotype)** mouse (IgG1)**References** Niedrig *et al.* 1991

- 111/052: Weak cross-reaction with HIV-2 on WB, otherwise not cross-reactive with HIV-2 or SIV MAC. Niedrig *et al.* [1991]

No. 48

**MAb ID** polyclonal**HXB2 Location** p24 (51–82)**Author Location** Gag (183–214 LAI)**Epitope** DLNTMLNTVGGHQAAMQMLKETINEEAAEWDR**Subtype** B**Neutralizing** no**Immunogen** vaccine*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* p24 Gag *Adjuvant:* QS21**Species (Isotype)** human (IgG)**References** Pialoux *et al.* 2001

- 28 subjects were vaccinated with six HIV-1 peptides that were selected to be particularly rich in CTL epitopes, presented in lipopeptides with or without adjuvant QS21 – HIV-specific Ab responses were detected in 25/28 (89%), proliferative in 19/28 (79%), and CTL in 13/24 (54%) of testable volunteers – only 4/28 had Ab responses to peptide G1, 4/28 had proliferative responses, and no patient had a CTL response. Pialoux *et al.* [2001]

No. 49

**MAb ID** 91-5**HXB2 Location** p24 (64–75)**Author Location** p24 (196–207)**Epitope** AAMQMLKETINE**Neutralizing** no**Immunogen** HIV-1 infection**Species (Isotype)** human (IgG1 $\lambda$ )**References** Gorny *et al.* 1998; Robinson *et al.* 1990b; Tyler *et al.* 1990; Gorny *et al.* 1989

- 91-5: NIH AIDS Research and Reference Reagent Program: 1238.
- 91-5: Did not enhance HIV-1 IIIB infection. Robinson *et al.* [1990b]
- 91-5: Synthesized by immortalization of peripheral blood cells with Epstein-Barr virus. Gorny *et al.* [1989]

No. 50

**MAb ID** 1109/01**HXB2 Location** p24 (69–86)**Author Location** p24 (201–218 BRU)**Epitope** LKETINEEAAEWDRVHPV**Neutralizing** no**Immunogen** vaccine*Strain:* B clade IIIB *HIV component:* HIV-1**Species (Isotype)** mouse (IgG)**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

No. 51

**MAb ID** 14D4E11**HXB2 Location** p24 (69–86)**Author Location** p24 (201–218 BRU)**Epitope** LKETINEEAAEWDRVHPV**Neutralizing** no**Immunogen** vaccine*Vector/Type:* purified HIV-1**Species (Isotype)** mouse (IgG1)**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Janvier *et al.* 1992; Janvier *et al.* 1990

- 14D4E11: Mapped to aa209-217 through Pepsan method (original paper, AAEWDRVHP) – cross-reacts with HIV-2 Janvier *et al.* [1990] and to aa203-217 through EIA pentadecapeptide Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

No. 52

**MAb ID** 1G5C8**HXB2 Location** p24 (69–86)**Author Location** p24 (201–218 BRU)**Epitope** LKETINEEAAEWDRVHPV**Neutralizing** no**Immunogen** vaccine*Vector/Type:* protein *HIV component:* p24 Gag**Species (Isotype)** mouse (IgG2b)**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Janvier *et al.* 1992; Janvier *et al.* 1990

- 1G5C8: Mapped to aa209-217 through Pepscan method (original paper, AAEWDRVHP) Janvier *et al.* [1990] and to aa203-217 through EIA pentadecapeptide Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

**No.** 53

**MAb ID** 47-2

**HXB2 Location** p24 (69–86)

**Author Location** p24 (201–218 BRU)

**Epitope** LKETINEEAAEWDVHPV

**Neutralizing** no

**Immunogen** vaccine

*Strain:* B clade BRU

**Species (Isotype)** mouse (IgG)

**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

**No.** 54

**MAb ID** 714/01

**HXB2 Location** p24 (69–86)

**Author Location** p24 (201–218 BRU)

**Epitope** LKETINEEAAEWDVHPV

**Neutralizing** no

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG)

**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

**No.** 55

**MAb ID** polyclonal

**HXB2 Location** p24 (69–86)

**Author Location** p24 (201–218 LAI)

**Epitope** LKETINEEAAEWDVHPV

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* Gag, p17 Gag, p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse

**References** Truong *et al.* 1997

- An ELISA assay was used to study a panel of Gag peptides – mature p24 CA epitopes mapped to residues 176-192, 201-218, 233-253, 285-304, and were recognized by antibodies elicited by rp24CA – one p17MA epitope, residues 11-25, and one p24CA epitope, residues 176-192, were recognized by antibodies raised against anti-p55 virus-like particles, suggesting a different antigenic properties for p24CA and p17MA antibodies depending on whether they are produced against the mature soluble protein or the immature assembled form of the gag proteins. Truong *et al.* [1997]

**No.** 56

**MAb ID** 111/073

**HXB2 Location** p24 (71–81)

**Author Location** p24 (203–213 IIIB)

**Epitope** ETINEEAAEWD

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag

**Species (Isotype)** mouse (IgG1)

**References** Niedrig *et al.* 1991

- 111/073: cross-reactive between HIV-1, HIV-2 and SIV MAC by multiple assays. Niedrig *et al.* [1991]

**No.** 57

**MAb ID** 113/038

**HXB2 Location** p24 (71–81)

**Author Location** p24 (203–213 IIIB)

**Epitope** ETINEEAAEWD

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag

**Species (Isotype)** mouse (IgG1)

**References** Niedrig *et al.* 1991

- 113/038: cross-reactive between HIV-1, HIV-2 and SIV MAC by multiple assays. Niedrig *et al.* [1991]

**No.** 58

**MAb ID** 1-E-4

**HXB2 Location** p24 (71–85)

**Author Location** p24 (203–217)

**Epitope** ETINEEAAEWDVHPV

**Neutralizing** no

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG)

**References** Niedrig *et al.* 1989

- 1-E-4: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]

**No.** 59

**MAb ID** 1-E-9

**HXB2 Location** p24 (71–85)

**Author Location** p24 (203–217)

**Epitope** ETINEEAAEWDVHPV

**Neutralizing** no

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG)

**References** Niedrig *et al.* 1989

- 1-E-9: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]

**No.** 60

**MAb ID** 10-E-7

**HXB2 Location** p24 (71–85)

**Author Location** p24 (203–217)

**Epitope** ETINEEAAEWDVHPV

**Neutralizing** no

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 10-E-7: One of nine MAbs that bind to this peptide – cross-reactive with HIV-2 ROD and SIV MAC. Niedrig *et al.* [1989]
- 10-E-7: Cross reactive between HIV-1, HIV-2 and SIV. Niedrig *et al.* [1988]

**No.** 61  
**MAb ID** 10-G-9  
**HXB2 Location** p24 (71–85)  
**Author Location** p24 (203–217)  
**Epitope** ETINEEAAEWDRVHP  
**Neutralizing** no  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 10-G-9: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]
- 10-G-9: HIV-1 specific. Niedrig *et al.* [1988]

**No.** 62  
**MAb ID** 11-C-5  
**HXB2 Location** p24 (71–85)  
**Author Location** p24 (203–217)  
**Epitope** ETINEEAAEWDRVHP  
**Neutralizing** no  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 11-C-5: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]
- 11-C-5: HIV-1 specific. Niedrig *et al.* [1988]

**No.** 63  
**MAb ID** 2-E-4  
**HXB2 Location** p24 (71–85)  
**Author Location** p24 (203–217)  
**Epitope** ETINEEAAEWDRVHP  
**Neutralizing** no  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG2a)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 2-E-4: One of nine MAbs that bind to this peptide – cross-reactive with HIV-2 ROD. Niedrig *et al.* [1989]
- 2-E-4: Cross reactive between HIV-1, HIV-2 and SIV by ELISA, HIV-1 and HIV-2 by WB. Niedrig *et al.* [1988]

**No.** 64  
**MAb ID** 2-H-4  
**HXB2 Location** p24 (71–85)  
**Author Location** p24 (203–217)  
**Epitope** ETINEEAAEWDRVHP

**Neutralizing** no  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 2-H-4: One of nine MAbs that bind to this peptide – cross-reactive with HIV-2 ROD. Niedrig *et al.* [1989]
- 2-H-4: Cross reactive between HIV-1, HIV-2 and SIV by ELISA, HIV-1 and HIV-2 by WB. Niedrig *et al.* [1988]

**No.** 65  
**MAb ID** 8-D-2  
**HXB2 Location** p24 (71–85)  
**Author Location** p24 (203–217)  
**Epitope** ETINEEAAEWDRVHP  
**Neutralizing** no  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG2a)  
**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 8-D-2: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]
- 8-D-2: HIV-1 specific. Niedrig *et al.* [1988]

**No.** 66  
**MAb ID** 8-G-9  
**HXB2 Location** p24 (71–85)  
**Author Location** p24 (203–217)  
**Epitope** ETINEEAAEWDRVHP  
**Neutralizing** no  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG)  
**References** Niedrig *et al.* 1989

- 8-G-9: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]

**No.** 67  
**MAb ID** 8-H-7  
**HXB2 Location** p24 (71–85)  
**Author Location** p24 (203–217)  
**Epitope** ETINEEAAEWDRVHP  
**Neutralizing** no  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG3)  
**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 8-H-7: One of nine MAbs that bind to this peptide. Niedrig *et al.* [1989]

**No.** 68  
**MAb ID** C5123

**HXB2 Location** p24 (71–85)  
**Author Location** p24 (203–217 HXB2)  
**Epitope** ETINEEAAEWDVHP  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* viral lysate *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1κ)  
**References** Hinkula *et al.* 1990

- C5123: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

**No.** 69

**MAb ID** 1-B-7  
**HXB2 Location** p24 (76–85)  
**Author Location** p24 (208–217 BH10)  
**Epitope** EAAEWDVHP  
**Neutralizing** no  
**Immunogen** vaccine

*Strain:* B clade IIIB

**Species (Isotype)** mouse (IgG1)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 1-B-7: Reacts with two overlapping peptides, region of overlap is given – reacted with HIV-2 and SIV MAC. Niedrig *et al.* [1989]

**No.** 70

**MAb ID** 3-B-7  
**HXB2 Location** p24 (76–85)  
**Author Location** p24 (208–217 BH10)  
**Epitope** EAAEWDVHP  
**Neutralizing** no  
**Immunogen** vaccine

*Strain:* B clade IIIB

**Species (Isotype)** mouse (IgG1)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 3-B-7: Reacts with two overlapping peptides, region of overlap is given – reacted with HIV-2. Niedrig *et al.* [1989]

**No.** 71

**MAb ID** 6-D-12  
**HXB2 Location** p24 (76–85)  
**Author Location** p24 (208–217 BH10)  
**Epitope** EAAEWDVHP  
**Neutralizing** no  
**Immunogen** vaccine

*Strain:* B clade IIIB

**Species (Isotype)** mouse (IgG1)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 6-D-12: Reacts with two overlapping peptides, region of overlap is given – reacted with HIV-2. Niedrig *et al.* [1989]

**No.** 72

**MAb ID** 6-E-7  
**HXB2 Location** p24 (76–85)  
**Author Location** p24 (208–217 BH10)  
**Epitope** EAAEWDVHP  
**Neutralizing** no

**Immunogen** vaccine  
*Strain:* B clade IIIB

**Species (Isotype)** mouse (IgG1)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 6-E-7: Reacts with two overlapping peptides, region of overlap is given – reacted with HIV-2 and SIV MAC. Niedrig *et al.* [1989]

**No.** 73

**MAb ID** 8-D-5  
**HXB2 Location** p24 (76–85)  
**Author Location** p24 (208–217 BH10)  
**Epitope** EAAEWDVHP  
**Neutralizing** no  
**Immunogen** vaccine

*Strain:* B clade IIIB

**Species (Isotype)** mouse (IgG)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988

- 8-D-5: Reacts with two overlapping peptides, region of overlap is given – bound only HIV-1. Niedrig *et al.* [1989]

**No.** 74

**MAb ID** FF1  
**HXB2 Location** p24 (76–90)  
**Author Location** p24 (208–222 HXB2)  
**Epitope** EAAEWDVHPVHAGP  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* inactivated HIV

**Species (Isotype)** mouse (IgG1κ)  
**References** Hinkula *et al.* 1990

- FF1: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

**No.** 75

**MAb ID** 113/072  
**HXB2 Location** p24 (81–90)  
**Author Location** p24 (213–222 IIIB)  
**Epitope** DRVHPVHAGP  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag

**Species (Isotype)** mouse (IgG1)  
**References** Niedrig *et al.* 1991

- 113/072: Weak cross-reaction with HIV-2 on WB, otherwise not cross-reactive with HIV-2 or SIV MAC. Niedrig *et al.* [1991]

**No.** 76

**MAb ID** 25.3  
**HXB2 Location** p24 (82–102)  
**Author Location** p24 (82–102)  
**Epitope** RVHPVHAGPIAPGQMREPRGS  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)** mouse (IgG1κ)  
**References** Momany *et al.* 1996

- 25.3: Crystal structure of the CA protein bound to Fab 25.3 was solved – monomers form 7 alpha-helices arranged in a coiled-coil – Fab binds to a long antigenic peptide that separates the longest helices, with a salt bridge at CA 82 R, and interactions as far away as positions 100 and 102. Momany *et al.* [1996]

**No.** 77

**MAb ID** 13-102-100

**HXB2 Location** p24 (84–94)

**Author Location** p24 (102–112 IIIB)

**Epitope** HPVHAGPIAPG

**Neutralizing**

**Immunogen**

**Species (Isotype)** mouse (IgG)

**Research Contact** Advanced Technologies, Inc., Columbia, MD

**References** Qian & Tomer 1998; Parker *et al.* 1996

- 13-102-100: Affinity capillary electrophoresis was used to fine map this epitope, and the optimal peptide was defined as VHAGPIAPGIAP – this method uses migration time shifts to probe relative affinities of Abs – the antibody binds to the cyclophilin A binding domain. Qian & Tomer [1998]
- 13-102-100: Binding site (HPVHAGPIAPG) defined by epitope footprinting – first binding p24 to MAb, then allowing proteolytic cleavage to take place to cleave unprotected residues, then performing mass spectrometry to identify protected residues of epitope. Parker *et al.* [1996]

**No.** 78

**MAb ID** RL4.72.1

**HXB2 Location** p24 (87–101)

**Author Location** p24 (219–233 BRU)

**Epitope** HAGPIAPGQMREPRG

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* D clade NDK *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG)

**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Tatsumi *et al.* 1990

- RL4.72.1: Immunized with inactivated HIV NDK, D clade, reacts with B clade peptide. Robert-Hebmann *et al.* [1992a]

**No.** 79

**MAb ID** 406/01

**HXB2 Location** p24 (101–121)

**Author Location** p24 (233–253 BRU)

**Epitope** GSIDIAGTTSTLQEIQGWMNTNN

**Neutralizing** no

**Immunogen** vaccine

*Strain:* B clade IIIB

**Species (Isotype)** mouse (IgG)

**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

**No.** 80

**MAb ID** polyclonal

**HXB2 Location** p24 (101–121)

**Author Location** p24 (233–253 LAI)

**Epitope** GSIDIAGTTSTLQEIQGWMNTNL

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* Gag, p17 Gag, p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse

**References** Truong *et al.* 1997

- An ELISA assay was used to study a panel of Gag peptides – mature p24 CA epitopes mapped to residues 176-192, 201-218, 233-253, 285-304, and were recognized by antibodies elicited by rp24CA – one p17MA epitope, residues 11-25, and one p24CA epitope, residues 176-192, were recognized by antibodies raised against anti-p55 virus-like particles, suggesting a different antigenic properties for p24CA and p17MA antibodies depending on whether they are produced against the mature soluble protein or the immature assembled form of the gag proteins. Truong *et al.* [1997]

**No.** 81

**MAb ID** 38:9.6K (38:96K)

**HXB2 Location** p24 (121–130)

**Author Location** p24 (253–262 HXB2)

**Epitope** NPPIPVGEIY

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* p24-p15 Gag

**Species (Isotype)** mouse (IgG1κ)

**References** Hinkula *et al.* 1990

- 38:9.6K: UK Medical Research Council AIDS reagent: ARP365.
- 38:9.6K: Called 38:96K – epitope defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

**No.** 82

**MAb ID** EB1A9

**HXB2 Location** p24 (121–135)

**Author Location** p24 (253–267 LAI)

**Epitope** NPPIPVGEIYKRWII

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1)

**Research Contact** R. B. Ferns and R. S. Tedder

**References** Ferns *et al.* 1989; Ferns *et al.* 1987

- EB1A9: UK Medical Research Council AIDS reagent: ARP345.
- EB1A9: Reacted with both p55 and p24 – showed less than 75% homologous inhibition. Ferns *et al.* [1987]

**No.** 83

**MAb ID** polyclonal

**HXB2 Location** p24 (121–152)

**Author Location** Gag (253–284 LAI)

**Epitope** NPPIPVGEIYKRWILGLNKIVRMYSPSILD

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* p24 Gag *Adjuvant:* QS21

**Species (Isotype)** human (IgG)

**References** Pialoux *et al.* 2001

- 28 subjects were vaccinated with six HIV-1 peptides that were selected to be particularly rich in CTL epitopes, presented in lipopeptides with or without adjuvant QS21 – HIV-specific Ab responses were detected in 25/28 (89%), proliferative in 19/28 (79%), and CTL in 13/24 (54%) of testable volunteers – 25/28 had Ab responses to peptide G2, 14/28 had proliferative responses, and CTL responses were detected. Pialoux *et al.* [2001]

**No.** 84

**MAb ID** 30:3E5

**HXB2 Location** p24 (141–170)

**Author Location** p24 (273–302 HXB2)

**Epitope** IVRMYSPSILDIRQGPKEPFRDYVDRFYK

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* p24-p15 Gag

**Species (Isotype)** mouse (IgG1λ)

**Research Contact** B. Wahren

**References** Hinkula *et al.* 1990

- 30:3E5: UK Medical Research Council AIDS reagent: ARP367.
- 30:3E5: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

**No.** 85

**MAb ID** EF7

**HXB2 Location** p24 (141–170)

**Author Location** p24 (273–302 HXB2)

**Epitope** IVRMYSPSILDIRQGPKEPFRDYVDRFYK

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* p24-p15 Gag

**Species (Isotype)** mouse (IgG1κ)

**References** Lundin *et al.* 1996; Hinkula *et al.* 1990

- EF7: UK Medical Research Council AIDS reagent: ARP366.
- EF7: Included as a control. Lundin *et al.* [1996]
- EF7: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53. Hinkula *et al.* [1990]

**No.** 86

**MAb ID** LH-104-E

**HXB2 Location** p24 (143–148)

**Author Location** p24 (275–280 BRU)

**Epitope** RMYSP

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BRU

**Species (Isotype)** mouse (IgG1κ)

**References** Haaheim *et al.* 1991

- LH-104-E: UK Medical Research Council AIDS reagent: ARP319.
- LH-104-E: Reacts with both p24 and p55. Haaheim *et al.* [1991]

**No.** 87

**MAb ID** 1B2C12

**HXB2 Location** p24 (149–154)

**Author Location** p24 (273–292 IIIB)

**Epitope** SILDIR

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* purified HIV-1

**Species (Isotype)** mouse (IgG1)

**References** Janvier *et al.* 1992; Janvier *et al.* 1990

- 1B2C12: Reacts with HIV-1 and HIV-2– mapped to aa281–286 through Pepsan method Janvier *et al.* [1990], and to aa273–292 through EIA pentadecapeptide method Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

**No.** 88

**MAb ID** LH-104-K

**HXB2 Location** p24 (149–154)

**Author Location** p24 (281–286 BRU)

**Epitope** SILDIR

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BRU

**Species (Isotype)** mouse (IgG1κ)

**References** Haaheim *et al.* 1991

- LH-104-K: UK Medical Research Council AIDS reagent: ARP322.
- LH-104-K: Binds exclusively with p24 (not p55) Haaheim *et al.* [1991]

**No.** 89

**MAb ID** LH-104-A

**HXB2 Location** p24 (152–157)

**Author Location** p24 (BRU)

**Epitope** DIRQGP+QGVGGP

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* p24 Gag

**Species (Isotype)** mouse (IgG1κ)

**References** Haaheim *et al.* 1991

- LH-104-A: UK Medical Research Council AIDS reagent: ARP307.
- LF-104-A: A 104 amino acid peptide was used to immunize mice – hexapeptide scans revealed two reactive p24 peptides – cross-competition studies indicated the region 270–286. Haaheim *et al.* [1991]

**No.** 90

**MAb ID** 1.17.3

**HXB2 Location** p24 (152–172)  
**Author Location** p24 (152–172 SIVmac)  
**Epitope** CVKQGPKEPFQSYVDRFYKSL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B clade AGM TYO-7 *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**References** Otteken *et al.* 1992  
 • 1.17.3: Recognized an epitope present on HIV-2/SIVmac (MAC251/32H) and HIV-2smmH4, but not SIVagmTYO-1, HIV-1 IIIB or SIVmnd. Otteken *et al.* [1992]

**No.** 91  
**MAb ID** 1A7  
**HXB2 Location** p24 (152–172)  
**Author Location** p24 (152–172 SIVmac)  
**Epitope** CVKQGPKEPFQSYVDRFYKSL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B clade AGM TYO-7 *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**References** Otteken *et al.* 1992  
 • 1A7: Recognized an epitope present on HIV-2/SIVmac (MAC251/32H) and HIV-2smmH4, but not SIVagmTYO-1, HIV-1 IIIB or SIVmnd. Otteken *et al.* [1992]

**No.** 92  
**MAb ID** 1F6  
**HXB2 Location** p24 (152–172)  
**Author Location** p24 (152–172 SIVmac)  
**Epitope** CVKQGPKEPFQSYVDRFYKSL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B clade AGM TYO-7 *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**References** Otteken *et al.* 1992  
 • 1F6: Recognized an epitope present on HIV-2/SIVmac (MAC251/32H) and HIV-2smmH4, but not SIVagmTYO-1, HIV-1 IIIB or SIVmnd. Otteken *et al.* [1992]

**No.** 93  
**MAb ID** 23A5G4  
**HXB2 Location** p24 (153–172)  
**Author Location** p24 (285–304 IIIB)  
**Epitope** IRQGPKEPFRDYVDRFYKTL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p24 Gag  
**Species (Isotype)** mouse (IgG1)  
**References** Janvier *et al.* 1996; Janvier *et al.* 1992; Janvier *et al.* 1990

• 23A5G4: A few sera which were able to bind the linear sequence 178–192, but not sequence 288–302 in an indirect peptide ELISA inhibited the binding of 23A5G4 to the native p24. Janvier *et al.* [1996]  
 • 23A5G4: Mapped to aa209–217 through Pepsan method Janvier *et al.* [1990] and to aa285–304 through EIA pentadecapeptide method Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]

**No.** 94  
**MAb ID** 23A5G5  
**HXB2 Location** p24 (153–172)  
**Author Location** p24 (285–304 BRU)  
**Epitope** IRQGPKEPFRDYVDRFYKTL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB *HIV component:* p24 Gag  
**Species (Isotype)** mouse (IgG)  
**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b

**No.** 95  
**MAb ID** 3D10G6  
**HXB2 Location** p24 (153–172)  
**Author Location** p24 (285–304 IIIB)  
**Epitope** IRQGPKEPFRDYVDRFYKTL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* purified HIV-1  
**Species (Isotype)** mouse (IgG1)  
**References** Janvier *et al.* 1992; Janvier *et al.* 1990  
 • 3D10G6: Epitope cross-reacts with HIV-1 and HIV-2–mapped to aa260–267 through Pepsan method Janvier *et al.* [1990] and to aa285–304 through EIA pentadecapeptide method. Janvier *et al.* [1990, 1992]

**No.** 96  
**MAb ID** polyclonal  
**HXB2 Location** p24 (153–172)  
**Author Location** p24 (285–304 LAI)  
**Epitope** IRQGPKEPFRDYVDRFYKTL  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* Gag, p17 Gag, p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (Isotype)** mouse

**References** Truong *et al.* 1997  
 • An ELISA assay was used to study a panel of Gag peptides – mature p24 CA epitopes mapped to residues 176–192, 201–218, 233–253, 285–304, and were recognized by antibodies elicited by rp24CA – one p17MA epitope, residues 11–25, and one p24CA epitope, residues 176–192, were recognized by antibodies raised against anti-p55 virus-like particles, suggesting a different antigenic properties for p24CA and p17MA antibodies depending on whether they are produced against the mature soluble protein or the immature assembled form of the gag proteins. Truong *et al.* [1997]



**No.** 97  
**MAb ID** F5-4  
**HXB2 Location** p24 (153–175)  
**Author Location** p24 (153–174 HXB2)  
**Epitope** IRQGPKEPFRDYVDRFYKTLRAE  
**Subtype** B  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)** mouse  
**References** Kusk *et al.* 1992; Kusk *et al.* 1988  
 • F5-4: Binds to a location in the most hydrophilic region of p24. Kusk *et al.* [1988, 1992]

**No.** 98  
**MAb ID** MO9.42.2  
**HXB2 Location** p24 (153–178)  
**Author Location** p24 (285–310 BRU)  
**Epitope** IRQGPKEPFRDYVDRFYKTLRAEQAS  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* virus *Strain:* HIV-2 ROD  
*HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG)  
**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b  
 • MO9.42.2: Reacts with HIV-1s, HIV-2s, and SIVs in rec protein ELISA. Robert-Hebmann *et al.* [1992b]

**No.** 99  
**MAb ID** MO9.50.2  
**HXB2 Location** p24 (153–178)  
**Author Location** p24 (285–310 BRU)  
**Epitope** IRQGPKEPFRDYVDRFYKTLRAEQAS  
**Neutralizing** no  
**Immunogen** vaccine  
*Strain:* HIV-2 ROD  
**Species (Isotype)** mouse (IgG)  
**References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b  
 • MO9.50.2: Reacts with HIV-1s, HIV-2s, and SIVs in rec protein ELISA. Robert-Hebmann *et al.* [1992b]

**No.** 100  
**MAb ID** V10  
**HXB2 Location** p24 (155–169)  
**Author Location** p24 (289–303 IIIB)  
**Epitope** QGPKEPFRDYVDRFY  
**Neutralizing** no  
**Immunogen** virus  
**Species (Isotype)** mouse  
**References** Matsuo *et al.* 1992  
 • V10: Reacts with HIV-1 and SIV AGM analogous peptides. Matsuo *et al.* [1992]

**No.** 101  
**MAb ID** V107  
**HXB2 Location** p24 (155–177)  
**Author Location** p24 (289–311 IIIB)  
**Epitope** QGPKEPFRDYVDRFYKTLRAEQA  
**Neutralizing** no

**Immunogen** virus  
**Species (Isotype)** mouse  
**References** Matsuo *et al.* 1992  
 • V107: Reacts with FIV, HIV-1 and SIV AGM analogous peptides. Matsuo *et al.* [1992]

**No.** 102  
**MAb ID** LH-104-C  
**HXB2 Location** p24 (156–161)  
**Author Location** p24 (BRU)  
**Epitope** GPKEPF+QGVGGP  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* p24 Gag  
**Species (Isotype)** mouse (IgG3κ)  
**References** Haaheim *et al.* 1991  
 • LH-104-C: UK Medical Research Council AIDS reagent: ARP309.  
 • LF-104-C: A 104 amino acid peptide was used to immunize mice – hexapeptide scans revealed two reactive p24 peptides – cross-competition studies indicated the region 351–373. Haaheim *et al.* [1991]

**No.** 103  
**MAb ID** 12-B-4  
**HXB2 Location** p24 (161–170)  
**Author Location** p24 (293–302 IIIB)  
**Epitope** FRDYVDRFYK  
**Neutralizing** no  
**Immunogen** vaccine  
*Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**References** Niedrig *et al.* 1989; Niedrig *et al.* 1988  
 • 12-B-4: Epitope is defined as the overlap between two HIV-1 reactive peptides – cross-reacts with HIV-2 ROD and SIV MAC. Niedrig *et al.* [1988, 1989]

**No.** 104  
**MAb ID** C5122  
**HXB2 Location** p24 (161–170)  
**Author Location** p24 (293–302 HXB2)  
**Epitope** FRDYVDRFYK  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* viral lysate *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1κ)  
**References** Hinkula *et al.* 1990  
 • C5122: Defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

**No.** 105  
**MAb ID** 9A4C4  
**HXB2 Location** p24 (170–188)  
**Author Location** p24 (303–317 IIIB)  
**Epitope** KTLRAEQASQEVKNWMTET  
**Neutralizing** no

- Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* p24 Gag
- Species (Isotype)** mouse (IgG1)
- References** Robert-Hebmann *et al.* 1992a; Robert-Hebmann *et al.* 1992b; Janvier *et al.* 1992; Janvier *et al.* 1990
- 9A4C4: Mapped to aa260-267 through Pepsan method Janvier *et al.* [1990] – and to aa303-317 through EIA pentadecapeptide method Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]
- No.** 106
- MAb ID** 11C10B10
- HXB2 Location** p24 (171–185)
- Author Location** p24 (303–317 IIIB)
- Epitope** TLRAEQASQEVKNWM
- Neutralizing** no
- Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p24 Gag
- Species (Isotype)** mouse (IgG1)
- References** Janvier *et al.* 1992; Janvier *et al.* 1990
- 11C10B10: Mapped to aa260-267 through Pepsan method Janvier *et al.* [1990] and to aa303-317 through EIA pentadecapeptide method Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]
- No.** 107
- MAb ID** 11D11F2
- HXB2 Location** p24 (171–185)
- Author Location** p24 (303–317 IIIB)
- Epitope** TLRAEQASQEVKNWM
- Neutralizing** no
- Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p24 Gag
- Species (Isotype)** mouse (IgG1)
- References** Janvier *et al.* 1992; Janvier *et al.* 1990
- 11D11F2: Mapped to aa260-267 through Pepsan method Janvier *et al.* [1990] and to aa303-317 through EIA pentadecapeptide method Janvier *et al.* [1992]. Janvier *et al.* [1990, 1992]
- No.** 108
- MAb ID** CD12B4
- HXB2 Location** p24 (171–185)
- Author Location** p24 (303–317 LAI)
- Epitope** TLRAEQASQEVKNWM
- Subtype** B
- Neutralizing** no
- Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1
- Species (Isotype)** mouse (IgG1)
- Research Contact** R. B. Ferns and R. S. Tedder
- References** Ferns *et al.* 1989; Ferns *et al.* 1987
- CD12B4: UK Medical Research Council AIDS reagent: ARP346.
- CD12B4: Reacted with both p55 and p24 – strain-specific binding. Ferns *et al.* [1987]
- No.** 109
- MAb ID** BE3
- HXB2 Location** p24 (176–190)
- Author Location** p24 (308–322 HXB2)
- Epitope** QASQEVKNWMTETLL
- Subtype** B
- Neutralizing** no
- Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p24-p15 Gag
- Species (Isotype)** mouse (IgG1κ)
- Research Contact** B. Wahren
- References** Hinkula *et al.* 1990
- BE3: UK Medical Research Council AIDS reagent: ARP368.
  - BE3: Defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]
- No.** 110
- MAb ID** L14
- HXB2 Location** p24 (176–190)
- Author Location** p24 (308–322 HXB2)
- Epitope** QASQEVKNWMTETLL
- Subtype** B
- Neutralizing** no
- Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p24-p15 Gag
- Species (Isotype)** mouse (IgG1κ)
- Research Contact** B. Wahren
- References** Hinkula *et al.* 1990
- L14: UK Medical Research Council AIDS reagent: ARP369.
  - L14: Defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]
- No.** 111
- MAb ID** 108/03
- HXB2 Location** p24 (181–190)
- Author Location** p24 (313–322 IIIB)
- Epitope** VKNWMTETLL
- Neutralizing** no
- Immunogen** vaccine  
*Vector/Type:* beta-galactosidase fusion protein *Strain:* B clade IIIB *HIV component:* p24 Gag
- Species (Isotype)** mouse (IgG1)
- References** Niedrig *et al.* 1991
- 108/03: Cross-reactive between HIV-1, HIV-2 and SIV MAC by multiple tests. Niedrig *et al.* [1991]
- No.** 112
- MAb ID** 110/015
- HXB2 Location** p24 (181–190)
- Author Location** p24 (313–322 IIIB)
- Epitope** VKNWMTETLL
- Neutralizing** no
- Immunogen** vaccine

*Vector/Type:* beta-galactosidase fusion protein  
*Strain:* B clade IIIB *HIV component:* p24 Gag

**Species (Isotype)** mouse (IgG1)

**References** Niedrig *et al.* 1991

- 110/015: Cross-reactive between HIV-1, HIV-2 and SIV MAC by multiple tests. Niedrig *et al.* [1991]

**No.** 113

**MAb ID** 32:32K

**HXB2 Location** p24 (199–222)

**Author Location** p24 (331–354 HXB2)

**Epitope** KTILKALGPAATLEEMMTACQGVG

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* p24-p15 Gag

**Species (Isotype)** mouse (IgG1 $\lambda$ )

**References** Hinkula *et al.* 1990

- 32:32K: UK Medical Research Council AIDS reagent: ARP368.
- 32:32K: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

**No.** 114

**MAb ID** C5200

**HXB2 Location** p24 (199–222)

**Author Location** p24 (331–354 HXB2)

**Epitope** KTILKALGPAATLEEMMTACQGVG

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* viral lysate

**Species (Isotype)** mouse (IgG1 $\kappa$ )

**References** Hinkula *et al.* 1990

- C5200: Epitope defined by peptide blocking of binding to native protein. Hinkula *et al.* [1990]

**No.** 115

**MAb ID** FH2

**HXB2 Location** p24 (201–215)

**Author Location** p24 (333–347 HXB2)

**Epitope** ILKALGPAATLEEMM

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* p24-p15 Gag

**Species (Isotype)** mouse (IgG1 $\kappa$ )

**References** Hinkula *et al.* 1990

- FH2: Defined by peptide blocking of binding to native protein – WB reactive with p53 and p24. Hinkula *et al.* [1990]

**No.** 116

**MAb ID** 13B5

**HXB2 Location** p24 (205–214)

**Author Location** p24 (205–213)

**Epitope** LGPAATLEEM

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* p24 Gag

**Species (Isotype)** mouse

**Ab Type** C-term

**Research Contact** bioMerieux

**References** Berthet-Colominas *et al.* 1999

- 13B5: Fab which was bound to p24 capsid for crystallization and study of p24's structure. Berthet-Colominas *et al.* [1999]

**No.** 117

**MAb ID** 106/01

**HXB2 Location** p24 (211–230)

**Author Location** p24 (343–362 IIIB)

**Epitope** LEEMMTACQGVGGPGHKARV

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* beta-galactosidase fusion protein  
*Strain:* B clade IIIB *HIV component:* p24 Gag

**Species (Isotype)** mouse (IgG1)

**References** Niedrig *et al.* 1991

- 106/01: Cross-reactive between HIV-1, HIV-2 and SIV MAC by multiple tests. Niedrig *et al.* [1991]

**No.** 118

**MAb ID** LH-104-B

**HXB2 Location** p24 (225–230)

**Author Location** p24 (357–362 BRU)

**Epitope** GHKARV

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BRU

**Species (Isotype)** mouse (IgG1 $\kappa$ )

**References** Haaheim *et al.* 1991

- LH-104-B: UK Medical Research Council AIDS reagent: ARP308.
- LH-104-B: Binds exclusively with p55 (not p24), in contrast to LH-104-I. Haaheim *et al.* [1991]

**No.** 119

**MAb ID** LH-104-I

**HXB2 Location** p24 (226–231)

**Author Location** p24 (358–363 BRU)

**Epitope** HKARVL

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BRU

**Species (Isotype)** mouse (IgG1 $\kappa$ )

**References** Haaheim *et al.* 1991

- LH-104-I: UK Medical Research Council AIDS reagent: ARP321.
- LH-104-I: Binds exclusively with p24 (not p55), in contrast to LH-104-B. Haaheim *et al.* [1991]

## IV-C-4 Gag p24-p2p7p1p6 Antibodies

**No.** 120  
**MAb ID** LH-104-G  
**HXB2 Location** p24-p2p7p1p6 (231–5)  
**Author Location** p24 (363–368 BRU)  
**Epitope** LAEAMS  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade BRU  
**Species (Isotype)** mouse (IgG1κ)  
**References** Haaheim *et al.* 1991  
 • LH-104-G database comment: This epitope overlaps the p24-p2 cleavage site.  
 • LH-104-G: UK Medical Research Council AIDS reagent: ARP320.  
 • LH-104-G: Reacts with both p24 and p55, in contrast to LH-104-I. Haaheim *et al.* [1991]

## IV-C-5 Gag p2p7p1p6 Antibodies

**No.** 121  
**MAb ID** i5B11  
**HXB2 Location** p2p7p1p6 (19–28)  
**Author Location** p7 (5–14)  
**Epitope** NFRNQRKIVK  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7 Gag  
**Species (Isotype)** rat (IgG2a)  
**References** Tanchou *et al.* 1995; Tanchou *et al.* 1994; Otake *et al.* 1994  
 • i5B11 database comment: i5B11 and 15B11 may be two names for the same MAb.  
 • i5B11: MAb reacts with NCp7, NCp15, and partially inhibits NCp7-tRNA interaction. Tanchou *et al.* [1995]  
 • i5B11: Epitope mapped by ELISA and BIAcore – inhibits NCp7 primer tRNA binding. Tanchou *et al.* [1994]

**No.** 122  
**MAb ID** EC6  
**HXB2 Location** p2p7p1p6 (45–54)  
**Author Location** p15 (408–417 HXB2)  
**Epitope** PRKKGCKWCKG  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p24-p15 Gag  
**Species (Isotype)** mouse (IgG2aκ)  
**References** Hinkula *et al.* 1990  
 • EC6: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53. Hinkula *et al.* [1990]

**No.** 123  
**MAb ID** M12  
**HXB2 Location** p2p7p1p6 (45–54)  
**Author Location** p15 (408–417 HXB2)

**Epitope** PRKKGCKWCKG  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p24-p15 Gag  
**Species (Isotype)** mouse (IgG1κ)  
**References** Hinkula *et al.* 1990  
 • M12 database comment: There is a p15 and a gp120 mouse MAb both called M12 and a human gp41 Fab M12.  
 • M12: Epitope defined by peptide blocking of binding to native protein – WB reactive with p53. Hinkula *et al.* [1990]

**No.** 124  
**MAb ID** DG8  
**HXB2 Location** p2p7p1p6 (66–81)  
**Author Location** p7 (52–67)  
**Epitope** RQANFLGKIWPSYKGR  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7 Gag  
**Species (Isotype)** mouse  
**References** Tanchou *et al.* 1995  
 • DG8: Binds proximal to the second zinc-finger, inhibits NCp7-tRNA interaction. Tanchou *et al.* [1995]

**No.** 125  
**MAb ID** EB5  
**HXB2 Location** p2p7p1p6 (66–81)  
**Author Location** p7 (52–67)  
**Epitope** RQANFLGKIWPSYKGR  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7 Gag  
**Species (Isotype)** mouse  
**References** Tanchou *et al.* 1995  
 • EB5: Binds proximal to the second zinc-finger – mutation at position 59 (Lys to Ser) results in 10-fold reduction in reactivity. Tanchou *et al.* [1995]

**No.** 126  
**MAb ID** HH3  
**HXB2 Location** p2p7p1p6 (66–81)  
**Author Location** p7 (52–67)  
**Epitope** RQANFLGKIWPSYKGR  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7 Gag  
**Species (Isotype)** mouse (IgG2b)  
**References** Tanchou *et al.* 1995; Tanchou *et al.* 1994  
 • HH3: Binds proximal to the second zinc-finger. Tanchou *et al.* [1995]  
 • HH3: Epitopes mapped by ELISA and BIAcore – does not inhibit NCp7 primer tRNA binding. Tanchou *et al.* [1994]

**No.** 127  
**MAb ID** AD2

**HXB2 Location** p2p7p1p6 (78–86)  
**Author Location** p7 (64–72)  
**Epitope** YKGRPGNFL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
 Gag  
**Species (Isotype)** mouse (IgG)  
**References** Tanchou *et al.* 1995  
 • AD2: Binds at C term of NCp7. Tanchou *et al.* [1995]

**No.** 128  
**MAb ID** CA5  
**HXB2 Location** p2p7p1p6 (78–86)  
**Author Location** p7 (64–72)  
**Epitope** YKGRPGNFL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
 Gag  
**Species (Isotype)** mouse (IgG)  
**References** Tanchou *et al.* 1995  
 • CA5: Binds at C term of NCp7. Tanchou *et al.* [1995]

**No.** 129  
**MAb ID** DF3  
**HXB2 Location** p2p7p1p6 (78–86)  
**Author Location** p7 (64–72)  
**Epitope** YKGRPGNFL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
 Gag  
**Species (Isotype)** mouse (IgG)  
**References** Tanchou *et al.* 1995  
 • DF3: Binds at C term of NCp7. Tanchou *et al.* [1995]

**No.** 130  
**MAb ID** EC3  
**HXB2 Location** p2p7p1p6 (78–86)  
**Author Location** p7 (64–72)  
**Epitope** YKGRPGNFL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
 Gag  
**Species (Isotype)** mouse (IgG)  
**References** Tanchou *et al.* 1995  
 • EC3: Binds at C term of NCp7. Tanchou *et al.* [1995]

**No.** 131  
**MAb ID** FC12  
**HXB2 Location** p2p7p1p6 (78–86)  
**Author Location** p7 (64–72)  
**Epitope** YKGRPGNFL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
 Gag  
**Species (Isotype)** mouse (IgG)

**References** Tanchou *et al.* 1995  
 • FC12: Binds at C term of NCp7, reacts with NCp15, inhibits NCp7-tRNA interaction. Tanchou *et al.* [1995]

**No.** 132  
**MAb ID** GE4  
**HXB2 Location** p2p7p1p6 (78–86)  
**Author Location** p7 (64–72)  
**Epitope** YKGRPGNFL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
 Gag  
**Species (Isotype)** mouse (IgG)  
**References** Tanchou *et al.* 1995  
 • GE4: Binds at C term of NCp7. Tanchou *et al.* [1995]

**No.** 133  
**MAb ID** JB7  
**HXB2 Location** p2p7p1p6 (78–86)  
**Author Location** p7 (64–72)  
**Epitope** YKGRPGNFL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
 Gag  
**Species (Isotype)** mouse (IgG)  
**References** Tanchou *et al.* 1995  
 • JB7: Binds at C term of NCp7. Tanchou *et al.* [1995]

**No.** 134  
**MAb ID** JF11  
**HXB2 Location** p2p7p1p6 (78–86)  
**Author Location** p7 (64–72)  
**Epitope** YKGRPGNFL  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
 Gag  
**Species (Isotype)** mouse (IgG1)  
**References** Tanchou *et al.* 1995; Tanchou *et al.* 1994  
 • JF11: Binds at C term of NCp7. Tanchou *et al.* [1995]  
 • JF11: Epitopes mapped by ELISA and BIAcore – does not inhibit NCp7 primer tRNA binding. Tanchou *et al.* [1994]

#### IV-C-6 Gag Antibodies

**No.** 135  
**MAb ID** 16/4/2  
**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* DNA with CMV promotor,  
 DNA with CMV/MCK hybrid promotor,  
 DNA with MCK promotor  
**Species (Isotype)**  
**References** Bojak *et al.* 2002a

- 16/4/2: The ability of three different promoters to induce Gag specific immune responses was compared. The cytomegalovirus (CMV) early gene promoter, which allows constitutive expression in different cells of host tissue, the tissue specific muscle creatine kinase (MCK) promoter, which may be restricted to differentiated, multinucleated myofibers and so safer, and a hybrid MCK/CMV promoter – intramuscular immunization of BALB/c mice utilizing the MCK promoter in combination with a codon optimized gag gene generated humoral (IgG1 (Th1) and IgG2a (Th2)) and CTL immune responses against HIV-1 Gag, however, the quantified immune parameters were clearly reduced as compared to CMV promoter-driven Gag expression. Bojak *et al.* [2002a]

**No.** 136

**MAb ID** 183-H12-5C

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Neutralizing** no

**Immunogen**

**Species (Isotype)** mouse (IgG1)

**Research Contact** Bruce Chesebro and Kathy Wehrly, Rocky Mountain Laboratories, Hamilton, Montana

**References** Wehrly & Chesebro 1997; Toohey *et al.* 1995; Chesebro *et al.* 1992

- 183-H12-5C: NIH AIDS Research and Reference Reagent Program: 3537.
- 183-H12-5C: Cross-reacts with HIV1 and HIV-2 p24, and SIV p27. Wehrly & Chesebro [1997]
- 183-H12-5C: Used as antigen capture reagent for p24 ELISA. Chesebro *et al.* [1992]; Toohey *et al.* [1995]

**No.** 137

**MAb ID** 241-D

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Neutralizing** no

**Immunogen**

**Species (Isotype)** human (IgG1 $\lambda$ )

**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrcr6.med.nyu) (NYU Med. Center)

**References** Robinson *et al.* 1991; Tyler *et al.* 1990; Gorny *et al.* 1989

- 241-D: MH AIDS Research and Reference Reagent program: 1244.
- 241-D: An antibody by this name is available in the NIH AIDS Research and Reference Reagent Program, and they refer to the papers Gorny *et al.* [1989]; Tyler *et al.* [1990]; Robinson *et al.* [1991], but no p24 MAb by this name is discussed in these papers. Gorny *et al.* [1989]; Robinson *et al.* [1991]; Tyler *et al.* [1990]

**No.** 138

**MAb ID** 2A6

**HXB2 Location** Gag

**Author Location** p17

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)**

**Research Contact** A. O. Arthur, Frederick Cancer Research and Development Center, Frederick, MD

**References** Pincus *et al.* 1998

- 2A6: Part of a panel of 17 MAbs used as controls testing for the dual specificity of MAb G11H3 for both p17 and mycoplasma. Pincus *et al.* [1998]

**No.** 139

**MAb ID** 5E2.A3k

**HXB2 Location** Gag

**Author Location** p24 (1–158 SF2)

**Epitope**

**Neutralizing** no

**Immunogen**

**Species (Isotype)** mouse (IgG1)

**Research Contact** Biodesign International, Kennebunk, Maine, USA

**References** Hochleitner *et al.* 2000a

- 5E2.A3k: The Ab binding site was studied with epitope excision (protein is bound in native conformation to immobilized MAb, then digested with proteolytic enzymes) and extraction (protein is digested then allowed to react with Ab), followed by mass spectroscopy, as well as lysine modification – the epitope is discontinuous, but involves the highly conserved N-term proline, and the antibody recognizes SIVs and HIV-2 as well as HIV-1 p24. Hochleitner *et al.* [2000a]

**No.** 140

**MAb ID** 71-31

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Neutralizing** no

**Immunogen**

**Species (Isotype)** human (IgG1 $\lambda$ )

**References** Bandres *et al.* 1998; Gorny *et al.* 1998; Gorny *et al.* 1997; Spear *et al.* 1993; Robinson *et al.* 1991; Robinson *et al.* 1990b; Gorny *et al.* 1989

- 71-31: NIH AIDS Research and Reference Reagent Program: 530.
- 71-31: Included as a negative control in studies that demonstrate that CXCR4 can bind to gp120 in the absence of CD4-gp120 interactions, and that this binding can be enhanced by Env deglycosylation. Bandres *et al.* [1998]
- 71-31: Did not mediate deposition of complement component C3 on HIV infected cells. Spear *et al.* [1993]
- 71-31: No enhancing or neutralizing activity. Robinson *et al.* [1991]
- 71-31: Did not enhance HIV-1 IIIB infection. Robinson *et al.* [1990b]

**No.** 141

**MAb ID** 91-6

**HXB2 Location** Gag

**Author Location** p24 (121–240 IIIB)

**Epitope**

**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**References** Robinson *et al.* 1990b; Gorny *et al.* 1989  
 • 91-6: NIH AIDS Research and Reference Reagent Program: 1239.  
 • 91-6: No enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b]

**No.** 142  
**MAb ID** 98-4.3  
**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**

**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**References** Robinson *et al.* 1991  
 • 98-4.3: No enhancing or neutralizing activity. Robinson *et al.* [1991]

**No.** 143  
**MAb ID** 98-4.9  
**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** mouse (IgG3 $\lambda$ )  
**References** Gorny *et al.* 1989

**No.** 144  
**MAb ID** AC2  
**HXB2 Location** Gag  
**Author Location** p7  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
**Species (Isotype)** mouse (IgG)  
**References** Tanchou *et al.* 1995  
 • AC2: Binds NCp7 independent of Zn fingers, does not react with NCp15. Tanchou *et al.* [1995]

**No.** 145  
**MAb ID** BC1071  
**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** mouse  
**Research Contact** Aalto BioReagents  
**References** Schonning *et al.* 1999  
 • BC1071: The stoichiometry of MAb neutralization was tested and MAb BC1071 was used in this study for virion quantification. Schonning *et al.* [1999]

**No.** 146

**MAb ID** BE10  
**HXB2 Location** Gag  
**Author Location** p7  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
**Species (Isotype)** mouse (IgG)  
**References** Tanchou *et al.* 1995  
 • BE10: Binding NCp7 requires Zn fingers, does not react with NCp15, inhibits NCp7-tRNA interaction. Tanchou *et al.* [1995]

**No.** 147  
**MAb ID** CD9  
**HXB2 Location** Gag  
**Author Location** p7  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
**Species (Isotype)** mouse (IgG)  
**References** Tanchou *et al.* 1995  
 • CD9: Binds NCp7 independent of Zn fingers, does not react with NCp15. Tanchou *et al.* [1995]

**No.** 148  
**MAb ID** CH9B2  
**HXB2 Location** Gag  
**Author Location** p17  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B clade CBL-1 *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**Research Contact** R. B. Ferns and R. S. Tedder  
**References** Ferns *et al.* 1989; Ferns *et al.* 1987  
 • CH9B2: UK Medical Research Council AIDS reagent: ARP349.  
 • CH9B2: Reactive against p18 and p55. Ferns *et al.* [1987]

**No.** 149  
**MAb ID** ED8  
**HXB2 Location** Gag  
**Author Location** p7  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p7  
**Species (Isotype)** mouse (IgG)  
**References** Tanchou *et al.* 1995  
 • ED8: Binds NCp7 independent of Zn fingers, does not react with NCp15. Tanchou *et al.* [1995]

**No.** 150  
**MAb ID** EH12E1

**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B  
 clade CBL-1 *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**Research Contact** R. B. Ferns and R. S. Tedder  
**References** Ferns *et al.* 1989; Ferns *et al.* 1987  
 • EH12E1: UK Medical Research Council AIDS reagent: ARP313.  
 • EH12E1: Reacted with p55 and p24 in WB. Ferns *et al.* [1987]

**No.** 151  
**MAb ID** G11G1  
**HXB2 Location** Gag  
**Author Location** p17  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** rat  
**References** Pincus *et al.* 1996; Shang *et al.* 1991  
 • G11G1: Immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but only if the antigen was expressed at the cell surface – ricin-G11G1 did not mediate cell killing. Pincus *et al.* [1996]

**No.** 152  
**MAb ID** G11H3  
**HXB2 Location** Gag  
**Author Location** p17  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**  
**References** Pincus *et al.* 1998; Shang *et al.* 1991  
 • G11H3: This MAb is cross-reactive between p17 and mycoplasma – this antibody binds strain specifically to the variable lipoprotein (Vlp) F of *M. hyorhinis*, in the region of the carboxy-terminal repeat CCGSTPTPEQGNQGGSTPTPE-QGNSQVSK – the p17 epitope is discontinuous, but p17 and Vlp F share the tetrapeptide SQVS. Pincus *et al.* [1998]

**No.** 153  
**MAb ID** HyHIV-19  
**HXB2 Location** Gag  
**Author Location** p17 (JMH1)  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* p17  
 Gag  
**Species (Isotype)** mouse (IgG1)  
**References** Ota *et al.* 1998; Liu *et al.* 1995  
 • HyHIV-19: Does not react with p17 peptides – Ka is  $3.7 \times 10^6$  M-1 for rec p17 – inhibited growth of HIV-1 JMH1 in MT-4 cells when added 24 hours after the initial culture. Ota *et al.* [1998]

**No.** 154  
**MAb ID** IE8G2  
**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B  
 clade CBL-1 *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**Research Contact** R. B. Ferns and R. S. Tedder  
**References** Ferns *et al.* 1989; Ferns *et al.* 1987  
 • IE8G2: UK Medical Research Council AIDS reagent: ARP347.  
 • IE8G2: Reacted with both p55 and p24 – broadly reactive – showed less than 75% homologous inhibition. Ferns *et al.* [1987]

**No.** 155  
**MAb ID** V7-8  
**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** mouse (IgG3κ)  
**References** Montefiori *et al.* 1991; Robinson *et al.* 1990b  
 • V7-8: NIH AIDS Research and Reference Reagent Program: 381.  
 • V7-8: Reacted with HIV-1IIIB, RF, and MN. Montefiori *et al.* [1991]  
 • V7-8: Did not enhance HIV-1 IIIB infection. Robinson *et al.* [1990b]

**No.** 156  
**MAb ID** anti-p24  
**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein, virus-like particle (VLP) *HIV component:* Gag, gp120, Nef, Pol  
**Species (Isotype)** mouse (IgG)  
**Research Contact** Intracel Co  
**References** Buonaguro *et al.* 2001  
 • anti-p24: HIV-1 pr55 gag-based virus-like particles (VLP) carrying Nef and Pol open reading frames, as well as gp120 of the clade A isolate 94UG018, were created using a Baculovirus expression system to package additional ORFS into the VLP – anti-V3 and anti-p24 Abs were used to assess the expression levels and Gag and gp120-TM were found to be expressed at comparable levels on the VLP. Buonaguro *et al.* [2001]

**No.** 157  
**MAb ID** human sera  
**HXB2 Location** Gag  
**Author Location** p24



**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**References** Binley *et al.* 1997b

- Retention of anti-Env antibodies and loss of anti-Gag antibodies during progression was studied, and suggested to be the result of the loss of T-cell help and the unique ability of Env to stimulate B cells even in a backdrop of declining CD4 cells, because of the ability of Env to bind to the CD4 molecule. Binley *et al.* [1997b]

**No.** 158  
**MAb ID** polyclonal  
**HXB2 Location** Gag  
**Author Location** Gag (LAI)  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with protein boost  
*Strain:* B clade LAI *HIV component:* Gag, Nef, Tat *Adjuvant:* IL-18

**Species (Isotype)** mouse  
**References** Billaut-Mulot *et al.* 2001

- DNA vaccinated BALB/c mice primed and boosted with a multiepitopic vaccine with IL18 showed lymphoproliferative and CTL responses – co-administration of IL18 increased T-cell responses but decreased anti-HIV Ab levels. Billaut-Mulot *et al.* [2001]

**No.** 159  
**MAb ID** polyclonal  
**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* gp120 depleted whole killed virus *Strain:* AG recombinant HZ321 *HIV component:* virus *Adjuvant:* Complete Freund's Adjuvant (CFA), CpG immunostimulatory sequence (ISS)

**Species (Isotype)** rat  
**References** Moss *et al.* 2000

- Lewis rats co-immunized with HIV-1 antigen in Freund's and with immunostimulatory sequences CpG stimulated increased IFN $\gamma$  expressing CD4+ and CD8+ T cells and anti-p24 antibodies relative to antigen in Freund's without CpG. Moss *et al.* [2000]

**No.** 160  
**MAb ID** polyclonal  
**HXB2 Location** Gag  
**Author Location** p24 (SF2)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF2  
*HIV component:* gp120, p24 Gag *Adjuvant:* MF59, PLG

**Species (Isotype)** mouse  
**References** O'Hagan *et al.* 2000

- Microparticles were used as an adjuvant for entrapped HIV-1 gp120 and induced strong serum IgG responses in mice – polylactide co-glycolide polymer (PLG) microparticles in combination with MF-59 had the highest Ab response and also induced p24 specific CTL. O'Hagan *et al.* [2000]

**No.** 161  
**MAb ID** polyclonal  
**HXB2 Location** Gag  
**Author Location** Gag (SF2)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA, protein *Strain:* B clade SF2 *HIV component:* Gag *Adjuvant:* aluminum phosphate, MF59, PLG  
**Species (Isotype)** macaque, guinea pig, mouse  
**References** O'Hagan *et al.* 2001

- DNA vaccines of codon-optimized Env and Gag genes driven by CMV promoters absorbed on to PLG microparticles were more effective than naked DNA at eliciting strong Ab responses (more rapid, higher titer, more stable), comparable to gp120 in MF-59. O'Hagan *et al.* [2001]

**No.** 162  
**MAb ID** polyclonal  
**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade *HIV component:* p24 Gag

**Species (Isotype)** rabbit (IgG)  
**References** Gupta *et al.* 2001

- Gag p24 is the mostly widely used HIV protein for serological based diagnostic kits — phage display libraries of HIV-1 p24 identified 2 epitope-rich regions: 70% of the clones that were identified using immunized rabbit sera had DNA fragments from the N-terminal region spanning 150–240 of Gag, and 30% from the carboxy-terminal region of p24 containing amino acids 310–360 — subtype B and C comparisons were made. Gupta *et al.* [2001]

**No.** 163  
**MAb ID** polyclonal  
**HXB2 Location** Gag  
**Author Location** p55  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* CD4BS, Gag, V3  
**Species (Isotype)** mouse

**References** Truong *et al.* 1996

- Antibodies raised against recombinant anti-p55 virus-like particles with the p24 region 196-226 deleted, bearing inserts of either the V3 or the CD4BS regions of gp120 were studied – no neutralizing responses, weak Env and strong Gag responses were elicited – the major homology region (MHR) and proximal sequences was found to be required for capsid assembly. Truong *et al.* [1996]

No. 164

MAB ID polyclonal

HXB2 Location Gag

Author Location p24 (LAI)

Epitope

Subtype B

Neutralizing

Immunogen vaccine

*Vector/Type:* peptide, virion, baculovirus, E. Coli recombinant protein *Strain:* B clade LAI *HIV component:* p24 Gag *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

Species (Isotype) rabbit (IgG)

References Devito *et al.* 2000c

- To compare vaccine strategies, rabbits were immunized with virion HIV-1/Lai, baculovirus recombinant p24, E. coli recombinant p24-15, and p24-derived peptides – the rabbit immunized with peptides had the broadest linear epitope responses – the capture ELISA method using anti-p24 IgG preparations was shown to capture isolates from HIV-1 subtypes or clades A to G – only immunization with virion HIV-1/Lai and baculovirus recombinant p24 developed IgG that was capable of efficiently capturing HIV-1 p24 in ELISA producing Abs able to recognise native configurations. Devito *et al.* [2000c]

No. 165

MAB ID polyclonal

HXB2 Location Gag

Author Location

Epitope

Neutralizing

Immunogen vaccine

*Vector/Type:* DNA *Adjuvant:* CpG immunostimulatory sequence (ISS), phosphorothioate oligodeoxynucleotides (ODNs)

Species (Isotype) mouse

References Deml *et al.* 2001

- Immunization mice with a codon-optimized Gag was compared with a non-optimized Rev dependent Gag expression vector – Gag expression was at higher levels and Rev independent with the codon-optimized Gag, and i.m. immunization gave a stronger Th1-driven humoral and cellular immune response – intradermal immunization with either Gag DNA induced a Th2 response and no CTL. Deml *et al.* [2001]

No. 166

MAB ID polyclonal

HXB2 Location Gag

Author Location

**Epitope**

Neutralizing yes

Immunogen HIV-1 infection

Species (Isotype) human

References Montefiori *et al.* 2001

- In 7/9 patients in whom HAART was initiated during early seroconversion, NAbs to autologous strains were not found immediately following treatment interruption after 1-3 years, and Env and Gag Abs were low or undetected by ELISA indicating, that early HAART suppresses the normal antibody response to HIV-1, presumably by limiting the concentration of viral antigens needed to drive B-cell maturation – in 3 patients with a viral rebound autologous NAbs rapidly appeared and correlated with spontaneous down-regulation of viremia – prolonged control of viremia after stopping treatment persisted in the absence of detectable NAbs, suggesting that cellular immune responses alone can control viremia under certain circumstances – these results support the notion that virus-specific B-cell priming, combined with CD8+ CTL induction, may be beneficial for HIV-1 vaccines that aim to suppress viremia in the absence of complete protection to prevent disease and reduce the rate of virus transmission. Montefiori *et al.* [2001]

No. 167

MAB ID polyclonal

HXB2 Location Gag

Author Location

Epitope

Neutralizing

Immunogen vaccine

*Vector/Type:* virus-like particle (VLP) *HIV component:* Env, Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)

Species (Isotype) mouse (IgG)

References Lebedev *et al.* 2000

- Virus-like particles (VLPs) in the form of spherical particles with yeast dsRNA enveloped in a polysaccharide matrix carrying the protein TBI, that contains fragments of HIV Env and Gag, were used to immunize BALB/c mice and induced specific Abs against HIV-1 as measured by ELISA with TBI. Lebedev *et al.* [2000]

No. 168

MAB ID polyclonal

HXB2 Location Gag

Author Location

Epitope

Neutralizing no

Immunogen vaccine

*Vector/Type:* DNA with CMV promoter, DNA with CMV/MCK hybrid promoter, DNA with MCK promoter

Species (Isotype) mouse (IgG1, IgG2a)

References Bojak *et al.* 2002a

- The ability of three different promoters to induce Gag specific immune responses was compared. The cytomegalovirus (CMV) early gene promoter, which allows constitutive expression in different cells of host tissue, the tissue specific muscle creatine kinase (MCK) promoter, which may be restricted

to differentiated, multinucleated myofibers and so safer, and a hybrid MCK/CMV promoter – intramuscular immunization of BALB/c mice utilizing the MCK promoter in combination with a codon optimized gag gene generated humoral (IgG1 (Th1) and IgG2a (Th2)) and CTL immune responses against HIV-1 Gag, however, the quantified immune parameters were clearly reduced as compared to CMV promoter-driven Gag expression. Bojak *et al.* [2002a]

**No.** 169

**MAb ID** polyclonal

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Meles *et al.* 2002

- Indeterminant WB in Ethiopians: of 12,124 specimens blood specimens from Ethiopia, 1,437 (11.9%) were HIV-1-positive for antibody, and 91 (0.8%) gave equivocal results, most often due to p24 reactivity – subsequent testing confirmed many of the indeterminants were HIV-negative – the American Red Cross diagnostic criteria was more accurate than CDC or WHO, which would have given some false positive results. Meles *et al.* [2002]

**No.** 170

**MAb ID** polyclonal

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Subtype** A

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP)

*Strain:* A clade UG5.94UG018 *HIV*

*component:* Gag, gp120

**Species (Isotype)** mouse

**References** Buonaguro *et al.* 2002

**Keywords** subtype comparisons

- BALB/c mice were immunized with VLPs carrying a subtype A gp120. Humoral immune responses directed against B-clade derived Gag (p24) peptides or gp120-Env V3 loop peptide were readily induced following a multi-dose immunization with VLP particles presenting a gp120 molecule from a HIV-1 isolate of clade A. VLP-immunized mice showed autologous and heterologous (against B-clade HIV-1 IIIB strain) neutralization activity. Proliferative responses and CTL were also observed. Buonaguro *et al.* [2002] (**subtype comparisons**)

**No.** 171

**MAb ID** polyclonal

**HXB2 Location** Gag

**Author Location** Gag

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Gag

**Species (Isotype)** mouse (IgG1)

**References** Bojak *et al.* 2002b

**Keywords** Th1

- Balb/c mice vaccinated by syngag, a DNA plasmid expressing HIV-1 Gag modified for human/mammalian codon usage, gave stronger and longer lasting immune responses than wild type gag. Gag-specific antibody and cellular immune responses were both increased, with a clear T-helper 1 polarization. There was a better IgG1/IgG2 response to intramuscular (i.m.) as compared to subcutaneous (s.c.) vaccination. Bojak *et al.* [2002b] (**Th1**)

**No.** 172

**MAb ID** polyclonal

**HXB2 Location** Gag

**Author Location** Gag

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* DNA, protein, virus-like particle (VLP), PLG microparticle *Adjuvant:* E. coli heat labile enterotoxin

**Species (Isotype)** macaque

**References** Otten *et al.* 2003

- This study evaluates different vaccine technologies that avoid live vectors including plasmid DNA, recombinant p55Gag protein or gag-pol administered by polylactide coglycolide (PLG) microparticles, LTK63 as adjuvant, VLP, and plasmid DNA. 4/4 macaques primed with Gag-PLG and LTK63 showed strong antibody responses after the fourth immunization at week six. The best CTL responses were found for gag DNA, the best Th and Ab were obtained using Gag protein on PLG microparticles; Gag DNA priming with a PLG-protein boost gave high level CTL, Th and Ab responses. Otten *et al.* [2003]

**No.** 173

**MAb ID** polyclonal

**HXB2 Location** Gag

**Author Location** p24

**Epitope**

**Subtype** multiple

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Barin *et al.* 2005

**Keywords** acute/early infection, assay development

- A combination of 4 antigenic regions was used to differentiate between early (<180 days) and chronic infection. These regions were: p24; the gp41 peptide spanning the immunodominant epitope (IDE) of gp41, RVAVERYLKDQQLGIWGCSGKICTTAV, and a subtype D version of this peptide; 5 V3 consensus peptides including A, B, C, D, and CRF01-AE; and Integrase. V3 and the IDE provide the best discrimination, with >20 fold higher levels in chronic infection when assayed by EIA using dried serum spots. Antibodies to Integrase and p24 were not as distinctive, and people tend to lose, not increase, responses to p24 over time. This assay can be

used to identify samples from early infection with high sensitivity and specificity. Barin *et al.* [2005] (**assay development, acute/early infection**)

**No.** 174  
**MAb ID** polyclonal  
**HXB2 Location** Gag  
**Author Location** Gag  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Lottersberger *et al.* 2004

- Addition of non-immunogenic side chains (AAAC and CAAA) to both N- and C-termini of synthetic alpha helical peptide sequences of HIV-1 p24 and p17 proteins improved Ab reactivity. As diminishing response to these antigens is a harbinger of progression these peptides may be useful in diagnostic assays. Lottersberger *et al.* [2004]

**No.** 175  
**MAb ID** polyclonal  
**HXB2 Location** Gag  
**Author Location** Gag  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with vaccinia boost  
*Strain:* Other *HIV component:* Gag  
**Species (Isotype)** mouse (IgA, IgG)  
**References** Huang *et al.* 2007b  
**Keywords** genital and mucosal immunity, mucosal immunity

- BALB/c mice were immunized with DNA plasmid and PEI/DNA complexes and boosted with recombinant TianTan vaccinia virus (rTTV) expressing HIV-1 Gag. PEI is polyethylenimine, a polymer with the high cationic charge density. HIV-specific IgG Abs in sera were comparable between DNA and PEI/DNA immunized mice. However, PEI/DNA stimulated significantly higher IgA responses than DNA alone in different mucosal secretions, both with or without rTTV boosting. Intramuscular rTTV boosting enhanced Ab immune responses raised by intranasal priming. Huang *et al.* [2007b] (**genital and mucosal immunity, mucosal immunity**)

**No.** 176  
**MAb ID** polyclonal  
**HXB2 Location** Gag  
**Author Location** Gag  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade HXB2  
*HIV component:* Gag  
**Species (Isotype)** macaque, mouse (IgA, IgG)  
**References** Chikhlikar *et al.* 2006  
**Keywords** vaccine antigen design

- DNA antigen encoding Gag as a chimera with the mouse and human lysosome-associated membrane protein (mLAMP/gag and hLAMP/gag) was used in immunization studies in mice and macaques. IgG responses in mice immunized with hLAMP/gag were considerably greater than the response to the mLAMP/gag. Strong HIV-specific IgG response was also observed in hLAMP/gag immunized macaques, which increased after each DNA immunization. Significant Gag-specific IgA levels were detected in 3 of 5 immunized macaques. Serum samples from the macaques recognized 13 of 49 20-aa Gag peptides covering Gag sequence indicating broad B-cell response. Chikhlikar *et al.* [2006] (**vaccine antigen design**)

**No.** 177  
**MAb ID** polyclonal HIVIG  
**HXB2 Location** Gag  
**Author Location** p24  
**Epitope**  
**Neutralizing P**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Nichols *et al.* 2002

- NYBC-HIVIG derived from patients with high NAb titers and NABI-HIVIG derived from patients with high anti-p24 Ab titers were compared in neutralizing assay against a panel of six primary isolates—both could neutralize all isolates tested but the NYBC-HIVIG dose required for 50% neutralization was of 3.2 fold lower, showing that the source plasmas influence the effective concentration of NAb present in HIVIG. Nichols *et al.* [2002]

#### IV-C-7 Protease Antibodies

**No.** 178  
**MAb ID** 1696  
**HXB2 Location** Protease (1–7)  
**Author Location** Protease (1–7 BH10)  
**Epitope** PQIYLWQ  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Protease  
**Species (Isotype)** mouse (IgG)  
**Ab Type** N-term  
**References** Lescar *et al.* 2003; Rezacova *et al.* 2002; Rezacova *et al.* 2001; Lescar *et al.* 1999

- **Keywords** review, structure
- 1696: Study compares the crystal structure of the scFv-1696 in the non-complexed form compared to the complexed Fab-1696 and the Ag-bound scFv-1696 structures. Changes in the three conformational tertiary structures of CDR-H3 as well as in the different relative orientations of the light-chain variable domains of the different structures were observed, demonstrating plasticity in the antibody binding site. Lescar *et al.* [2003] (**structure**)

- 1696: Review of the implications of antibody structure and antigen peptide binding for the mechanisms of inhibition of protease activity by two MABs with different binding sites in protease. Rezacova *et al.* [2002] (**review, structure**)
- 1696: The crystal structure of the single chain Fv fragment of 1696 bound to a cross-reactive peptide (PQITLWQRR) was obtained. This structure suggests that 1696 inhibits protease activity by favoring dissociation of the active homodimer. Rezacova *et al.* [2001] (**structure**)
- 1696: MAB binds to HIV-1 and HIV-2, putative epitopes are PQIYLWQ and PQFSLWK respectively – Pro1 is critical, QIYLWQR residues 2-8, does not compete - MAB disrupts catalytic activity – crystal structure of the ligand-free Fab at 3 Å resolution reveals a deep cavity lined by acidic and hydrophobic residues – the binding region is located within the region required for dimerization and the Fab structure could serve as a basis for drug design targeting this region. Lescar *et al.* [1999] (**structure**)

**No.** 179  
**MAb ID** 10E7  
**HXB2 Location** Protease (36–46)  
**Author Location** Protease (38–45 HXB2)  
**Epitope** MSLPGRWKPKM  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Protease  
**Species (Isotype)** hamster (IgG)  
**References** Bjorling *et al.* 1992; Croix *et al.* 1993  
 • 10E7: Immunodominant region of protease in Armenian hamster (but only weakly reactive in people, see: Bjorling *et al.* [1992]) – peptide MSLPGRWKP blocks protease binding Croix *et al.* [1993]. Bjorling *et al.* [1992]; Croix *et al.* [1993]

**No.** 180  
**MAb ID** F11.2.32  
**HXB2 Location** Protease (36–46)  
**Author Location** Protease (36–46 BH10)  
**Epitope** MSLPGRWKPKM  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* Protease  
**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** flap region  
**References** Rezacova *et al.* 2002; Lescar *et al.* 1999; Lescar *et al.* 1997; Lescar *et al.* 1996

- Keywords** review, structure
- F11.2.32: Review of the implications of antibody structure and antigen peptide binding for the mechanisms of inhibition of protease activity by two MABs with different binding sites in protease. Rezacova *et al.* [2002] (**review, structure**)
  - F11.2.32: Crystal structure of a Fab peptide complex was obtained. Distortion may occur in the flap region of the protein, important for regulating access of substrate to the catalytic site. Lescar *et al.* [1999] (**structure**)

- F11.2.32: Binding leads to significant inhibition in proteolytic activity – crystal structure of Fab-peptide was determined to 2.2 Å resolution – bound peptide shows no structural similarity to the corresponding segment in native protease suggesting binding may distort protein structure. Lescar *et al.* [1997] (**structure**)

**No.** 181  
**MAb ID** 13E1  
**HXB2 Location** Protease (38–45)  
**Author Location** Protease (38–45 HXB2)  
**Epitope** LPGRWKPK  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Protease  
**Species (Isotype)** hamster (IgG)  
**References** Croix *et al.* 1993  
 • 13E1: Binds to MSLPGRWKPKM with slightly higher affinity. Croix *et al.* [1993]

**No.** 182  
**MAb ID** 8B11  
**HXB2 Location** Protease (38–45)  
**Author Location** Protease (38–45 HXB2)  
**Epitope** LPGRWKPK  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Protease  
**Species (Isotype)** hamster (IgG)  
**References** Croix *et al.* 1993  
 • 8B11: Binds to MSLPGRWKPKM with slightly higher affinity. Croix *et al.* [1993]

**No.** 183  
**MAb ID** 8C10  
**HXB2 Location** Protease (38–45)  
**Author Location** Protease (38–45 HXB2)  
**Epitope** LPGRWKPK  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Protease  
**Species (Isotype)** hamster (IgG)  
**References** Croix *et al.* 1993  
 • 8C10: Binds to MSLPGRWKPKM with slightly higher affinity. Croix *et al.* [1993]

**No.** 184  
**MAb ID** 8G5  
**HXB2 Location** Protease (38–45)  
**Author Location** Protease (38–45 HXB2)  
**Epitope** LPGRWKPK  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine



*Vector/Type:* protein *HIV component:* Protease

**Species (Isotype)** hamster (IgG)

**References** Croix *et al.* 1993

- 8G5: Binds to MSLPGRWKPKM with slightly higher affinity. Croix *et al.* [1993]

## IV-C-8 RT Antibodies

**No.** 185

**MAb ID** 1E8

**HXB2 Location** RT (65–73)

**Author Location** RT (65–73)

**Epitope** KKDSTKWRK

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT  
*Adjuvant:* nitrocellulose

**Species (Isotype)** mouse (IgG1)

**References** Gu *et al.* 1996; Wu *et al.* 1993

- 1E8: Significantly inhibits DNA polymerase activity of RT by hindering binding of dNTPs – additive or synergistic RT inhibition with nevirapine and delavirdine. Gu *et al.* [1996]
- 1E8: Inhibits RT activity, binding site overlaps with two AZT resistance mutations. Wu *et al.* [1993]

**No.** 186

**MAb ID** polyclonal

**HXB2 Location** RT (249–263)

**Author Location** RT (249–263)

**Epitope** KDSWTVNDIQKLVGK

**Neutralizing**

**Immunogen** vaccine, *in vitro* stimulation or selection

*Vector/Type:* peptide presented on icosahedral protein scaffold *HIV component:* RT  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** human (IgG)

**Ab Type** gp120 C2

**References** Domingo *et al.* 2003

**Keywords** vaccine antigen design

- A virus-like protein scaffold, called E2DISP, derived from pyruvate dehydrogenase multienzyme from *Bacillus stearothermophilus* has been engineered to display 60 copies of one or more epitopes on a single molecule. An E2DISP scaffold which displayed pep23, a 15-residue B and T helper HIV-1 RT epitope elicited a pep23-specific T-helper response *in vitro*. The E2DISP scaffold displaying peptide RT2, which is a CTL HIV-1 RT epitope, was able to elicit a CD8+ T cell response *in vitro* and in a vaccinated HLA-A2 transgenic mouse. Thus the E2DISP scaffold allows cell-entry and access to both the class I and class II processing pathways. The Th response in vaccinated mice supported Pep23-specific IgG responses. Domingo *et al.* [2003] (**vaccine antigen design**)

**No.** 187

**MAb ID** 1.152 B3

**HXB2 Location** RT (294–302)

**Author Location** RT (294–302)

**Epitope** PLTEEAEELE

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**References** Orvell *et al.* 1991

- 1.152 B3: Weakly positive by immunofluorescence – binding inhibits RT enzymatic activity. Orvell *et al.* [1991]

**No.** 188

**MAb ID** 1.158 E2

**HXB2 Location** RT (294–302)

**Author Location** RT (294–302)

**Epitope** PLTEEAEELE

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**References** Orvell *et al.* 1991

- 1.158 E2: Negative by immunofluorescence – binding inhibits RT enzymatic activity. Orvell *et al.* [1991]

**No.** 189

**MAb ID** 31D6

**HXB2 Location** RT (294–318)

**Author Location** RT (294–319)

**Epitope** PLTEEAEELELAENREILKEPVHGVY

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* E. coli Trp fusion protein *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**References** Szilvay *et al.* 1992

- 31D6: Strong inhibitor of RT, > 50% inhibition. Szilvay *et al.* [1992]

**No.** 190

**MAb ID** 31G8

**HXB2 Location** RT (294–318)

**Author Location** RT (294–319)

**Epitope** PLTEEAEELELAENREILKEPVHGVY

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* E. coli Trp fusion protein *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**References** Szilvay *et al.* 1992

- 31G8: Weak inhibitor of RT, reactive by immunofluorescence. Szilvay *et al.* [1992]

**No.** 191

**MAb ID** 32E7

**HXB2 Location** RT (294–318)

**Author Location** RT (294–319)

**Epitope** PLTEEAEELELAENREILKEPVHGVY

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* E. coli Trp fusion protein *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**References** Szilvay *et al.* 1992

- 32E7: Weak inhibitor of RT, reactive by immunofluorescence. Szilvay *et al.* [1992]

**No.** 192

**MAb ID** 33D5

**HXB2 Location** RT (294–318)

**Author Location** RT (294–319)

**Epitope** PLTEEALELAENREILKEPVHGVY

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* E. coli Trp fusion protein *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**References** Szilvay *et al.* 1992

- 33D5: Weak inhibitor of RT, reactive by immunofluorescence. Szilvay *et al.* [1992]

**No.** 193

**MAb ID** 5B2

**HXB2 Location** RT (294–318)

**Author Location** RT (294–319)

**Epitope** PLTEEALELAENREILKEPVHGVY

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* E. coli Trp fusion protein *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**References** Szilvay *et al.* 1992

- 5B2: UK Medical Research Council AIDS reagent: ARP3018.
- 5B2: There is an RT specific Ab Szilvay *et al.* [1992] and a gp41 specific Ab Tian *et al.* [2001] both called 5B2. Szilvay *et al.* [1992]
- 5B2: Weak inhibitor of RT, reactive by immunofluorescence. Szilvay *et al.* [1992]

**No.** 194

**MAb ID** polyclonal

**HXB2 Location** RT (295–304)

**Author Location** RT (295–304 PV22)

**Epitope** LTEEALELA

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**References** Grimison & Laurence 1995

**No.** 195

**MAb ID** 1.153 G10

**HXB2 Location** RT (350–354)

**Author Location** RT (350–354)

**Epitope** KTGKY

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**References** Orvell *et al.* 1991

**No.** 196

**MAb ID** RTMAb8

**HXB2 Location** RT (376–383)

**Author Location** RT (532–539)

**Epitope** TTESIVIW

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT

**Species (Isotype)** mouse (IgG)

**References** Ferns *et al.* 1991; Tisdale *et al.* 1988

**No.** 197

**MAb ID** 1D4A3

**HXB2 Location** RT (384–387)

**Author Location** RT (540–543)

**Epitope** GKIP

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT

**Species (Isotype)** mouse (IgG)

**References** Ferns *et al.* 1991

**No.** 198

**MAb ID** RT6H

**HXB2 Location** RT (384–387)

**Author Location** RT (540–543)

**Epitope** GKIP

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT

**Species (Isotype)** mouse (IgG)

**References** Ferns *et al.* 1991

**No.** 199

**MAb ID** 1.160 B3

**HXB2 Location** RT (442–450)

**Author Location** RT (442–450)

**Epitope** VDGAANRET

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**References** Orvell *et al.* 1991

**No.** 200

**MAb ID** polyclonal

**HXB2 Location** RT (521–531)

**Author Location** RT (521–531 PV22)

**Epitope** IIEQLIKKEKV

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**References** Grimison & Laurence 1995

**No.** 201

**MAb ID** C2003

**HXB2 Location** RT (536–549)

**Author Location** RT (703–716 BH10)

**Epitope** VPAHKGIGGNEQVD

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BH10  
**Species (Isotype)** rabbit (IgG)

**References** DeVico *et al.* 1991

- C2003: Inhibits polymerase activity from a variety of retroviruses – RT protected from inhibition by preincubation with template primer. DeVico *et al.* [1991]

## IV-C-9 Integrase Antibodies

**No.** 202

**MAb ID** 1C4

**HXB2 Location** Integrase (1–16)

**Author Location** Integrase (1–16 HXB2)

**Epitope** FLDGIDKAQDEHEKYH

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade HXB2

*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** N-term

**References** Nilsen *et al.* 1996; Haugan *et al.* 1995

- 1C4: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 1C4: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

**No.** 203

**MAb ID** 2C11

**HXB2 Location** Integrase (1–16)

**Author Location** Integrase (1–16 HXB2)

**Epitope** FLDGIDKAQDEHEKYH

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade HXB2

*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** N-term

**References** Nilsen *et al.* 1996

- 2C11: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]

**No.** 204

**MAb ID** 2E3

**HXB2 Location** Integrase (1–16)

**Author Location** Integrase (1–16 HXB2)

**Epitope** FLDGIDKAQDEHEKYH

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade HXB2

*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** N-term

**References** Ovod *et al.* 1992; Nilsen *et al.* 1996

- 2E3: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 2E3: There are two MAbs called 2E3 – the other one binds to Nef. Ovod *et al.* [1992]

**No.** 205

**MAb ID** 3E11

**HXB2 Location** Integrase (1–16)

**Author Location** Integrase (1–16 HXB2)

**Epitope** FLDGIDKAQDEHEKYH

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade HXB2

*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** N-term

**References** Nilsen *et al.* 1996; Otteken *et al.* 1992

- 3E11: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 3E11: There is another MAb with this ID that recognizes p17. Otteken *et al.* [1992]
- 3E11: Recognized an epitope present on HIV-2/SIVmac, SIVagm, HIV-1, and SIVmd. Otteken *et al.* [1992]

**No.** 206

**MAb ID** 3F9

**HXB2 Location** Integrase (1–16)

**Author Location** Integrase (1–16 HXB2)

**Epitope** FLDGIDKAQDEHEKYH

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade HXB2

*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** N-term

**References** Nilsen *et al.* 1996

- 3F9: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]

**No.** 207

**MAb ID** 5F8

**HXB2 Location** Integrase (1–16)

**Author Location** Integrase (1–16 HXB2)

**Epitope** FLDGIDKAQDEHEKYH



**Subtype B**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** N-term

**References** Nilsen *et al.* 1996; Haugan *et al.* 1995

- 5F8: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 5F8: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

**No.** 208  
**MAb ID** 6G5  
**HXB2 Location** Integrase (1–16)  
**Author Location** Integrase (1–16 HXB2)  
**Epitope** FLDGIDKAQDEHEKYH  
**Subtype B**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** N-term

**References** Nilsen *et al.* 1996

- 6G5: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]

**No.** 209  
**MAb ID** 7B6  
**HXB2 Location** Integrase (1–16)  
**Author Location** Integrase (1–16 HXB2)  
**Epitope** FLDGIDKAQDEHEKYH  
**Subtype B**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** N-term

**References** Nilsen *et al.* 1996

- 7B6: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]

**No.** 210  
**MAb ID** 7C6  
**HXB2 Location** Integrase (1–16)  
**Author Location** Integrase (1–16 HXB2)  
**Epitope** FLDGIDKAQDEHEKYH  
**Subtype B**

**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** N-term

**References** Nilsen *et al.* 1996

- 7C6: One of a large set of MAbs that interact with the N-terminal part of integrase: 1C4, 2C11, 2E3, 3E11, 3F9, 5F8, 6G5, 7B6, 7C6 – these MAbs inhibit end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]

**No.** 211  
**MAb ID** 6C5  
**HXB2 Location** Integrase (17–38)  
**Author Location** Integrase (17–38 HXB2)  
**Epitope** SNWRAMASDFNLPPVVAKEIVA  
**Subtype B**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** N-term

**References** Nilsen *et al.* 1996; Haugan *et al.* 1995

- 6C5: This MAb inhibits end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 6C5: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

**No.** 212  
**MAb ID** 8G4  
**HXB2 Location** Integrase (22–31)  
**Author Location** Integrase (12–42 HXB2)  
**Epitope** MASDFNLPPV+GYIEAEVIPAETGQETAYFI?  
**Subtype B**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)  
**References** Nilsen *et al.* 1996; Haugan *et al.* 1995

- 8G4: This MAb reacted strongly with peptides IN(12-31) and IN(22-42), and less strongly with peptide IN(82-101) – it did not react with a deletion mutant of positions 17-38 – this MAb inhibits end processing and DNA joining, but had little effect on integration activities. Nilsen *et al.* [1996]
- 8G4: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

**No.** 213  
**MAb ID** 17 (mAb17)  
**HXB2 Location** Integrase (25–35)  
**Author Location** Integrase (25–35)  
**Epitope** DFNLPPVVAKE  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Int

**Species (Isotype)** mouse (IgG1)

**References** Yi *et al.* 2000; Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994

- 17: Epitope mapped to helix-turn-helix motif in the N-term domain of Integrase, positions 25-35 – Zn binding stabilizes the Integrase-mAb17 complex – both MAb and Fab form of mAb17 inhibit Integrase activity – epitope region likely to be involved in protein-protein interaction. Yi *et al.* [2000]
- 17: Used for the creation of single chain variable antibody fragments (SFvs) for internal cellular expression – neutralization of IN activity prior to integration, whether the Ab is expressed in the nucleolus or the cytoplasm – relative binding affinity to IN: 12 > 17 = 33 > 21 > 4. Levy-Mintz *et al.* [1996]
- 17: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – the Zn finger motif is in the binding region – MAbs 14 and 17 form a competition group. Bizub-Bender *et al.* [1994]

**No.** 214

**MAb ID** 4D6

**HXB2 Location** Integrase (42–55)

**Author Location** Integrase (42–55 HXB2)

**Epitope** KCQLKGEAMHGQVD

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** N-term

**References** Nilsen *et al.* 1996; Haugan *et al.* 1995

- 4D6: This MAb inhibits end processing and DNA joining, and reduces reintegration activity. Nilsen *et al.* [1996]
- 4D6: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

**No.** 215

**MAb ID** 7-16 (7-19)

**HXB2 Location** Integrase (50–159)

**Author Location** Integrase (50–159 HXB2)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int

**Species (Isotype)** mouse (IgG2b)

**Ab Type** Integrase catalytic core

**Research Contact** Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan

**References** Ishikawa *et al.* 1999

- 7-16: Binds to the central catalytic domain – the paper seems to sometimes call this antibody 7-16, sometimes 7-19, a possible typo. Ishikawa *et al.* [1999]

**No.** 216

**MAb ID** 4F6

**HXB2 Location** Integrase (56–102)

**Author Location** Integrase (56–102 HXB2)

**Epitope** CSPGIWQLDCTHLEGGKLVILVAVHVASGYIEAE-VIPAETGQETAYFLL

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** Integrase catalytic core

**References** Nilsen *et al.* 1996; Haugan *et al.* 1995

- 4F6: MAb binding had minimal effects on IN *in vitro* activities. Nilsen *et al.* [1996]
- 4F6: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

**No.** 217

**MAb ID** anti-K159

**HXB2 Location** Integrase (151–163)

**Author Location** Integrase (163–175)

**Epitope** VESMNKELKKIIG

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* Int

**Species (Isotype)** rabbit (IgG)

**References** Maksutov *et al.* 2002; Maroun *et al.* 1999

- anti-K159: This epitope is similar to a fragment of the human protein Apoptosis regulator BCL-W (KIAA0271), ESNVKE-MEPLVGQV. Maksutov *et al.* [2002]
- anti-K159: Both the peptide K159, SQGVVESMNKELKKI-IGQVRDQAEHLKTA, and the Abs raised against this peptide inhibit Integrase activity – K159 was found to fulfill condition of minimal number of helical heptads to achieve the formation of a stable coiled-coil structure – Integrase is proposed to function as a dimer interacting in this region. Maroun *et al.* [1999]

**No.** 218

**MAb ID** 5D9

**HXB2 Location** Integrase (186–250)

**Author Location** Integrase (186–250 HXB2)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** Integrase DNA binding domain

**References** Nilsen *et al.* 1996; Haugan *et al.* 1995

- 5D9: MAb binding had minimal effects on IN *in vitro* activities. Nilsen *et al.* [1996]
- 5D9: While C-term and N-term anti-Integrase MAbs interfere with Integrase-DNA binding, 5D9 which binds more centrally, does not. Haugan *et al.* [1995]

**No.** 219

**MAb ID** 8-6

**HXB2 Location** Integrase (211–227)

**Author Location** Integrase (211–227 HXB2)

**Epitope** KELQKQITKIQNFRVYY  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int  
**Species (Isotype)** mouse (IgG1)  
**Research Contact** Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan  
**References** Ishikawa *et al.* 1999  
 • 8-6: Antibody binds proximal to the DNA binding region. Ishikawa *et al.* [1999]

**No.** 220  
**MAb ID** 19 (2-19, scAb2-19)  
**HXB2 Location** Integrase (228–236)  
**Author Location** Integrase (228–236 LAI)  
**Epitope** RDSRNPLWK  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Int  
**Species (Isotype)** mouse (IgG1)  
**References** Kitamura *et al.* 1999; Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994  
 • 19: Called 2-19, scAb2-19 is a single-chain Ab made from MAb 2-19 –acts intra-cellularly to block infection at low MOI by binding to integrase – scAb interfered with the folding of Gag-Pol polyprotein, the Ab did not affect viral production in LAI transfected cells, but the virus produced was less infectious – authors suggest that the epitope may be conformational. Kitamura *et al.* [1999]  
 • 19: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – 19 has a low binding affinity. Bizub-Bender *et al.* [1994]

**No.** 221  
**MAb ID** 2-19  
**HXB2 Location** Integrase (228–236)  
**Author Location** Integrase (228–236 HXB2)  
**Epitope** RDSRNPLWK  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int  
**Species (Isotype)** mouse (IgG2b)  
**Ab Type** Integrase DNA binding domain  
**Research Contact** Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan  
**References** Ishikawa *et al.* 1999  
 • 2-19: MAb inhibits RT-Integrase interaction, and the terminal cleavage and strand transfer functions of Integrase, but not the disintegration activity. Ishikawa *et al.* [1999]

**No.** 222  
**MAb ID** 8-22  
**HXB2 Location** Integrase (237–252)  
**Author Location** Integrase (237–252 HXB2)  
**Epitope** GPAKLLWKGEHAVVIQ  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** Integrase DNA binding domain  
**Research Contact** Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan  
**References** Ishikawa *et al.* 1999  
 • 8-22: MAb inhibits the terminal cleavage and strand transfer functions of Integrase, but not the disintegration activity. Ishikawa *et al.* [1999]

**No.** 223  
**MAb ID** 4-20  
**HXB2 Location** Integrase (253–261)  
**Author Location** Integrase (253–261 HXB2)  
**Epitope** DNSDIKVVVP  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** Integrase DNA binding domain  
**Research Contact** Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan  
**References** Ishikawa *et al.* 1999  
 • 4-20: Inhibits the terminal cleavage and strand transfer functions of Integrase, but not the disintegration activity. Ishikawa *et al.* [1999]

**No.** 224  
**MAb ID** 6-19  
**HXB2 Location** Integrase (262–270)  
**Author Location** Integrase (261–270 HXB2)  
**Epitope** RRKAKIIRD  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* chimeric maltose binding protein (MBP) *Strain:* B clade IIIB *HIV component:* Int  
**Species (Isotype)** mouse (IgG2b)  
**Ab Type** Integrase DNA binding domain  
**Research Contact** Yoshihiro Kitamura, Div of Mol Genetics, Nat Inst of Infectious Diseases, Musashimurayama, Japan  
**References** Ishikawa *et al.* 1999

- 6-19: Inhibits the terminal cleavage and strand transfer functions of Integrase, but not the disintegration activity. Ishikawa *et al.* [1999]

**No.** 225  
**MAb ID** 7C3  
**HXB2 Location** Integrase (262–271)  
**Author Location** Integrase (262–271 HXB2)  
**Epitope** RRKAKIIRDY  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**References** Nilsen *et al.* 1996; Haugan *et al.* 1995

- 7C3: A set of three MAbs recognize an epitope in this region, 7C3, 7F11, and 8E5 – all three HIV-1 MAbs cross-react with HIV-2 IN – these MAbs inhibit end-processing, DNA joining and reintegration, and had little effect on disintegration. Nilsen *et al.* [1996]
- 7C3: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

**No.** 226  
**MAb ID** 7F11  
**HXB2 Location** Integrase (262–271)  
**Author Location** Integrase (262–271 HXB2)  
**Epitope** RRKAKIIRDY  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**References** Lasky *et al.* 1987; Nilsen *et al.* 1996

- 7F11: A set of three MAbs recognize an epitope in this region, 7C3, 7F11, and 8E5 – all three HIV-1 MAbs cross-react with HIV-2 IN – these MAbs inhibit end-processing, DNA joining and reintegration, and had little effect on disintegration. Nilsen *et al.* [1996]
- 7F11: There is another MAb with this name that binds to gp120. Lasky *et al.* [1987]

**No.** 227  
**MAb ID** 8E5  
**HXB2 Location** Integrase (262–271)  
**Author Location** Integrase (262–271 HXB2)  
**Epitope** RRKAKIIRDY  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade HXB2  
*HIV component:* Int

**Species (Isotype)** mouse (IgG1κ)

**References** Nilsen *et al.* 1996; Haugan *et al.* 1995

- 8E5: A set of three MAbs recognize an epitope in this region, 7C3, 7F11, and 8E5 – all three HIV-1 MAbs cross-react with HIV-2 IN – these MAbs inhibit end-processing, DNA joining and reintegration, and had little effect on disintegration. Nilsen *et al.* [1996]
- 8E5: MAb interferes with integrase binding to DNA. Haugan *et al.* [1995]

**No.** 228  
**MAb ID** MAb 35  
**HXB2 Location** Integrase (264–273)  
**Author Location** Integrase (264–273)  
**Epitope** KAKIIRDY GK  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Int

**Species (Isotype)** mouse (IgGκ)

**References** Acel *et al.* 1998; Barsov *et al.* 1996

- MAb 35: Integrase was shown to have intrinsic DNA polymerase activity that can catalyze gap repair – MAb 35 inhibits this activity. Acel *et al.* [1998]
- MAb 35: There appears to be two different IN Abs with similar names: MAb 35 and 35. Barsov *et al.* [1996]
- MAb 35: Although MAb 35 does not inhibit HIV-1 IN, Fab 35 inhibits 3'-end processing, strand transfer and disintegration. Barsov *et al.* [1996]

## IV-C-10 Pol Antibodies

**No.** 229  
**MAb ID** 12  
**HXB2 Location** Pol  
**Author Location** Integrase (1–58)  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Int

**Species (Isotype)** mouse (IgG2a)

**References** Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994

- 12: Used for the creation of single-chain variable antibody fragments (SFVs) for internal cellular expression – neutralization of IN activity prior to integration, whether the Ab is expressed in the nucleolus or the cytoplasm – relative binding affinity to IN: 12 > 17 = 33 > 21 > 4. Levy-Mintz *et al.* [1996]
- 12: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – the Zn finger motif is in the binding region – MAbs 12, 13 and 35 form a competition group. Bizub-Bender *et al.* [1994]

**No.** 230  
**MAb ID** 13  
**HXB2 Location** Pol  
**Author Location** Integrase (1–58)  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Int  
**Species (Isotype)** mouse (IgG1)

**References** Bizub-Bender *et al.* 1994

- 13: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – the Zn finger motif is in the binding region – MAbs 12, 13 and 35 form a competition group. Bizub-Bender *et al.* [1994]

**No.** 231

**MAb ID** 14

**HXB2 Location** Pol

**Author Location** Integrase (1–58)

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Int

**Species (Isotype)** mouse (IgG1)

**References** Bizub-Bender *et al.* 1994

- 14: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – the Zn finger motif is in the binding region – MAbs 14 and 17 form a competition group. Bizub-Bender *et al.* [1994]

**No.** 232

**MAb ID** 16

**HXB2 Location** Pol

**Author Location** Integrase

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Int

**Species (Isotype)** mouse (IgG2a)

**References** Bizub-Bender *et al.* 1994

- 16: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized. Bizub-Bender *et al.* [1994]

**No.** 233

**MAb ID** 1C12B1

**HXB2 Location** Pol

**Author Location** RT (431–521)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT

**Species (Isotype)** mouse

**References** Ferns *et al.* 1991

- 1C12B1: UK Medical Research Council AIDS reagent: ARP384.
- 1C12B1: Recognized both p66 and p51 in Western blot, binds to C terminus. Ferns *et al.* [1991]

**No.** 234

**MAb ID** 21

**HXB2 Location** Pol

**Author Location** Integrase (58–141)

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Int

**Species (Isotype)** mouse (IgG2b)

**References** Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994

- 21: Used for the creation of single chain variable antibody fragments (SFvs) for internal cellular expression – neutralization of IN activity prior to integration, whether the Ab is expressed in the nucleolus or the cytoplasm – relative binding affinity to IN: 12 > 17 = 33 > 21 > 4. Levy-Mintz *et al.* [1996]
- 21: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized. Bizub-Bender *et al.* [1994]

**No.** 235

**MAb ID** 32 (mAb32, Fab32)

**HXB2 Location** Pol

**Author Location** Integrase (223–266)

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Int

**Species (Isotype)** mouse (IgG2b)

**References** Yi *et al.* 2002; Yi & Skalka 2000; Bizub-Bender *et al.* 1994

- 32: Called mAb32 – mAb33 and mAb32 compete for binding to the C-term domain of Integrase – while mAb32 only weakly inhibits IN activity, mAb33 inhibits strongly, mAb32 has a lower affinity than mAb33, and Fab32 does not inhibit at all while Fab33 inhibits DNA binding a catalytic activity. Yi *et al.* [2002]
- 32: Limited proteolysis combined with mass spectrometric analysis indicates Fab32 binds to two strands of the beta sheet, beta1 223F, 224R, 226Y, and 228R and beta5 264K and 266K. Yi & Skalka [2000]
- 32: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – MAbs 32 and 33 form a competition group. Bizub-Bender *et al.* [1994]

**No.** 236

**MAb ID** 35

**HXB2 Location** Pol

**Author Location** Integrase (1–58)

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Int

**Species (Isotype)** mouse (IgG2b)

**References** Bizub-Bender *et al.* 1994

- 35: There appears to be two IN Abs with similar names: MAb 35 and 35. Bizub-Bender *et al.* [1994]
- 35: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – the Zn finger motif is in the binding region – MAbs 12, 13 and 35 form a competition group. Bizub-Bender *et al.* [1994]

**No.** 237

**MAb ID** 3D12

**HXB2 Location** Pol  
**Author Location** RT  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type: vaccinia HIV component: RT*  
**Species (Isotype)** mouse (IgG2a)  
**References** Chiba *et al.* 1997  
 • 3D12: There is an anti-Nef MAb that also has this name (see Chiba *et al.* [1997]) Chiba *et al.* [1997]

**No.** 238  
**MAb ID** 3F10  
**HXB2 Location** Pol  
**Author Location** RT  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type: vaccinia HIV component: RT*  
**Species (Isotype)** mouse (IgG2a)  
**References** Chiba *et al.* 1997

**No.** 239  
**MAb ID** 4  
**HXB2 Location** Pol  
**Author Location** Integrase (141–172)  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type: protein HIV component: Int*  
**Species (Isotype)** mouse (IgG2b)  
**References** Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994

- 4: Used for the creation of single chain variable antibody fragments (SFvs) for internal cellular expression – neutralization of IN activity prior to integration, whether the Ab is expressed in the nucleolus or the cytoplasm – relative binding affinity to IN: 12 > 17 = 33 > 21 > 4. Levy-Mintz *et al.* [1996]
- 4: There is another MAb with this ID that reacts with gp41. Bizub-Bender *et al.* [1994]
- 4: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – 4 has a low binding affinity. Bizub-Bender *et al.* [1994]

**No.** 240  
**MAb ID** 5B11  
**HXB2 Location** Pol  
**Author Location** RT (BH-10)  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Research Contact** Amon Hizi, Sackler School of Medicine, Tel Aviv, Isreal  
**References** Herschhorn *et al.* 2003  
**Keywords** antibody generation, antibody sequence variable domain, immunotherapy

- 5B11: One of five human single chain Fv (ScFv) Abs isolated from an phage display library. F-6 was shown to the carboxyl terminal segment of the p66 RT polypeptide, corresponding to RNase H. F-6 inhibited the DNA and RNA-dependent DNA polymerase (RDDP) activities of HIV-1 RT; two others, 6E9 and 5B11, inhibited RDDP and so have possible therapeutic potential. Herschhorn *et al.* [2003] (**antibody generation, immunotherapy, antibody sequence variable domain**)

**No.** 241  
**MAb ID** 6B10  
**HXB2 Location** Pol  
**Author Location** RT (BH-10)  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Research Contact** Amon Hizi, Sackler School of Medicine, Tel Aviv, Isreal  
**References** Herschhorn *et al.* 2003  
**Keywords** antibody generation, antibody sequence variable domain

- 6B10: One of five human single chain Fv (ScFv) Abs isolated from an phage display library. F-6 was shown to the carboxyl terminal segment of the p66 RT polypeptide, corresponding to RNase H. F-6 inhibited the DNA and RNA-dependent DNA polymerase (DDDP and RDDP) activities of HIV-1 RT; two others, 6E9 and 5B11, inhibited RDDP and so have possible therapeutic potential. In contrast, 6B10 seemed to enhance DDDP activity and did not effect RDDP. Herschhorn *et al.* [2003] (**antibody generation, antibody sequence variable domain**)

**No.** 242  
**MAb ID** 6B9  
**HXB2 Location** Pol  
**Author Location** RT  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type: vaccinia HIV component: RT*  
**Species (Isotype)** mouse (IgG2a)  
**References** Chiba *et al.* 1997

**No.** 243  
**MAb ID** 6E9  
**HXB2 Location** Pol  
**Author Location** RT (BH-10)  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** in vitro stimulation or selection  
**Species (Isotype)** human  
**Research Contact** Amon Hizi, Sackler School of Medicine, Tel Aviv, Isreal  
**References** Herschhorn *et al.* 2003  
**Keywords** antibody generation, antibody sequence variable domain, immunotherapy

- 6E9: One of five human single chain Fv (ScFv) Abs isolated from an phage display library. F-6 was shown to the carboxyl terminal segment of the p66 RT polypeptide, corresponding to RNase H. F-6 inhibited the DNA and RNA-dependent DNA polymerase (RDDP) activities of HIV-1 RT; two others, 6E9 and 5B11, inhibited RDDP and so have possible therapeutic potential. Herschhorn *et al.* [2003] (**antibody generation, immunotherapy, antibody sequence variable domain**)

No. 244

**MAb ID** 7C4

**HXB2 Location** Pol

**Author Location** RT

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* vaccinia *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**References** Chiba *et al.* 1997

- 7C4: Dose-dependent inhibition of polymerase activity of RT of strains IIIIB, Bru and IMS-1, but not HIV-2 strains GH-1 or LAV-2 or SIV strains MAC or MND. Chiba *et al.* [1997]

No. 245

**MAb ID** E-4

**HXB2 Location** Pol

**Author Location** RT (BH-10)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Research Contact** Amon Hizi, Sackler School of Medicine, Tel Aviv, Isreal

**References** Herschhorn *et al.* 2003

**Keywords** antibody generation, antibody sequence variable domain

- E-4: One of five human single chain Fv (ScFv) Abs isolated from an phage display library. F-6 was shown to the carboxyl terminal segment of the p66 RT polypeptide, corresponding to RNase H. F-6 inhibited the DNA and RNA-dependent DNA polymerase (RDDP) activities of HIV-1 RT; two others, 6E9 and 5B11, inhibited RDDP and so have possible therapeutic potential. In contrast, E-4 seemed to enhance RDDP. Herschhorn *et al.* [2003] (**antibody generation, antibody sequence variable domain**)

No. 246

**MAb ID** RT-4

**HXB2 Location** Pol

**Author Location** RT

**Epitope**

**Neutralizing** no

**Immunogen**

**Species (Isotype)** mouse (IgG2b)

**References** Gu *et al.* 1996; Li *et al.* 1993

- RT-4: Increased nevirapine and delavirdine inhibition, no effect on AZT inhibition. Gu *et al.* [1996]

No. 247

**MAb ID** RT7O

**HXB2 Location** Pol

**Author Location** RT (231–315)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT

**Species (Isotype)** mouse (IgG1)

**Research Contact** B. Ferns and R. Tedder

**References** Ferns *et al.* 1991

- RT7O: UK Medical Research Council AIDS reagent: ARP381.
- RT7O: Conformational epitope located centrally in the protein – inhibited RT enzyme activity and thus may bind close to the active site of the enzyme. Ferns *et al.* [1991]

No. 248

**MAb ID** RT7U

**HXB2 Location** Pol

**Author Location** RT (231–315)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* RT

**Species (Isotype)** mouse

**Research Contact** B. Ferns and R. Tedder

**References** Ferns *et al.* 1991

- RT7U: UK Medical Research Council AIDS reagent: ARP380.
- RT7U: Has a conformational epitope – reacts with p66 and p51 in WB. Ferns *et al.* [1991]

No. 249

**MAb ID** anti-HIV-1 RT

**HXB2 Location** Pol

**Author Location** RT

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** mouse (IgG)

**References** Wainberg & Gu 1995; Maciejewski *et al.* 1995; di Marzo Veronese *et al.* 1986

- anti-HIV-1 RT: Cloned heavy and light chains to express Fab intracellularly, preventing HIV infection *in vitro* – this MAb was broadly cross-reactive with clinical strains and even HIV-2. Maciejewski *et al.* [1995]
- Commentary on Maciejewski *et al.* Wainberg & Gu [1995]

No. 250

**MAb ID** polyclonal

**HXB2 Location** Pol

**Author Location** p55

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP) *HIV component:* Gag, gp120, V3

**Species (Isotype)** macaque

**References** Wagner *et al.* 1998b

- A VLP is a non-infectious virus-like particle self-assembled from HIV Pr55 gag – macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains – gag and env CTL specific CTL were stimulated in each case, and Ab response to gag and gp120 and was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4 – despite the CTL and Ab response, immunized macaques were infected by interavenous challenge with SHIV chimeric challenge stock. Wagner *et al.* [1998b]

No. 251

**MAb ID** polyclonal

**HXB2 Location** Pol

**Author Location** RT

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12

**Species (Isotype)** mouse

**References** Kim *et al.* 1997b

- A gag/pol, vif or CMN160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice, as well as Ab response detected by ELISA. Kim *et al.* [1997b]

No. 252

**MAb ID** polyclonal

**HXB2 Location** Pol

**Author Location** RT (203–219)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* Salmonella *HIV component:* RT

**Species (Isotype)** mouse (IgA)

**References** Burnett *et al.* 2000

- A live attenuated bacterial vaccine, Salmonella SL3261-pHART, with an inserted HIV RT gene fragment in the Lpp-OmpA-HIV fusion protein, induced a lymphoproliferative Th response and fecal RT-specific IgA in BALB/c mice. Burnett *et al.* [2000]

No. 253

**MAb ID** polyclonal

**HXB2 Location** Pol

**Author Location** Integrase

**Epitope**

**Subtype** multiple

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 V3

**References** Barin *et al.* 2005

**Keywords** acute/early infection, assay development

- A combination of 4 antigenic regions was used to differentiate between early (<180 days) and chronic infection. These regions were: p24; the gp41 peptide spanning the immunodominant epitope (IDE) of gp41, RVAVERYLKDQQLGIWGC-SGKICTTAV, and a subtype D version of this peptide; 5 V3 consensus peptides including A, B, C, D, and CRF01-AE; and Integrase. V3 and the IDE provide the best discrimination, with >20 fold higher levels in chronic infection when assayed by EIA using dried serum spots. Antibodies to Integrase and p24 were not as distinctive, and people tend to lose, not increase, responses to p24 over time. Integrase antibodies are among the last to appear after infection. This assay can be used to identify samples from early infection with high sensitivity and specificity. Barin *et al.* [2005] (**assay development, acute/early infection**)

No. 254

**MAb ID** 33 (mAb33, Fab33, 33D5, mab 33)

**HXB2 Location** Pol

**Author Location** Integrase (223–268 HXB2)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Int

**Species (Isotype)** mouse (IgG2b)

**Ab Type** C-term

**References** Schreiber *et al.* 2005; Yi *et al.* 2002; Yi & Skalka 2000; Levy-Mintz *et al.* 1996; Bizub-Bender *et al.* 1994

**Keywords** antibody binding site definition and exposure, computational epitope prediction, mimotopes, structure

- 33: Called Fab33. A new computer program designed to recognize conformational epitopes in 3D structures that correspond to linear peptide mimotopes (3DEX) was tested using the known conformational epitope of this Fab. 223F, 224R, 226Y, 244K, 267I, and 268I, previously defined as the epitope from NMR structural studies (Yi2002) were confirmed, along with two additional amino acids, (A265 and K266). Schreiber *et al.* [2005] (**antibody binding site definition and exposure, mimotopes, computational epitope prediction, structure**)
- 33: Called mAb33 – mAb33 and mAb32 compete for binding to the C-term domain of Integrase – while mAb32 only weakly inhibits IN activity, mAb33 inhibits strongly, mAb32 has a lower affinity than mAb33, and Fab32 does not inhibit at all while Fab33 inhibits catalytic activity and DNA binding – heteronuclear NMR indicated eight residues of Integrase are immobilized upon Fab33 binding, two in the core of the protein, and 6 on the outer face that form a contiguous patch likely to contain the epitope – 223F, 224R, 226Y, 244K, 267I, and 268I, which may be a useful target for drug design – the Fab33-IN complex is far more soluble than IN alone and may be useful for crystallization. Yi *et al.* [2002] (**antibody binding site definition and exposure**)
- 33: Limited proteolysis combined with mass spectrometric analysis were used to define the binding site for Fab32, but Fab33 binding to the Integrase C-term domain left it resistant to proteolytic digestion. Yi & Skalka [2000]



- 33: Used for the creation of single chain variable antibody fragments (SFVs) for internal cellular expression – neutralization of IN activity prior to integration, whether the Ab is expressed in the nucleolus or the cytoplasm – relative binding affinity to IN: 12 > 17 = 33 > 21 > 4. Levy-Mintz *et al.* [1996]
- 33: BALBc mice were immunized with rec integrase, hybridomas expressing anti-integrase Abs were generated, and the antibodies characterized – MAbs 32 and 33 form a competition group. Bizub-Bender *et al.* [1994]

**No.** 255

**MAb ID** F-6

**HXB2 Location** Pol

**Author Location** RT (BH-10)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** in vitro stimulation or selection

**Species (Isotype)** human

**Ab Type** C-term

**Research Contact** Amon Hizi, Sackler School of Medicine, Tel Aviv, Isreal

**References** Herschhorn *et al.* 2003

**Keywords** antibody generation, antibody sequence variable domain, immunotherapy

- F-6: One of five human single chain Fv (ScFv) Abs isolated from an phage display library. F-6 was shown to bind to the carboxyl terminal segment of the p66 RT polypeptide, corresponding to RNase H. F-6 inhibited the DNA and RNA-dependent DNA polymerase (RDDP) activities of HIV-1 RT; two others, 6E9 and 5B11, inhibited RDDP and so have possible therapeutic potential. To pinpoint the mechanism of inhibition, three peptides were synthesized corresponding to the CDR3 sequences of F-6, and a cyclic version of the CDR H3 region bound to purified RT and blocked RDDP. Herschhorn *et al.* [2003] (**antibody generation, immunotherapy, antibody sequence variable domain**)

**No.** 256

**MAb ID** 6B9

**HXB2 Location** Pol

**Author Location** RT (155–250)

**Epitope**

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade

HXB2 *HIV component:* RT

**Species (Isotype)** mouse (IgG)

**Ab Type** RT palm domain

**References** Ohba *et al.* 2001; Chiba *et al.* 1997; Chiba *et al.* 1996

- 6B9: In contrast to MAb 7C4, which binds to the thumb region of RT, 6B9 binds to the palm subdomain and does not inhibit RT activity. Chiba *et al.* [1996]

**No.** 257

**MAb ID** 5F

**HXB2 Location** Pol

**Author Location** RT (252–335)

**Epitope**

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade

HXB2 *HIV component:* RT

**Species (Isotype)** mouse

**Ab Type** RT thumb domain

**References** Ohba *et al.* 2001

- 5F: BALB/c mice were vaccinated with vaccinia carrying RT and a phage display library was produced and panned with RT – Fabs 5F and 5G were cloned, both recognizing an immunodominant neutralizing RT epitope in the region of the template primer-binding site in the thumb domain also recognized by MAb 7C4 – sequencing revealed the heavy chains and light chains of 7C4, 5G and 7C4 are related. Ohba *et al.* [2001]

**No.** 258

**MAb ID** 5G

**HXB2 Location** Pol

**Author Location** RT (252–335)

**Epitope**

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade

HXB2 *HIV component:* RT

**Species (Isotype)** mouse

**Ab Type** RT thumb domain

**References** Ohba *et al.* 2001

- 5G: BALB/c mice were vaccinated with vaccinia carrying RT and a phage display library was produced and panned with RT – Fabs 5F and 5G were cloned, both recognizing an immunodominant neutralizing RT epitope in the region of the template primer-binding site in the thumb domain also recognized by MAb 7C4 – sequencing revealed the heavy chains and light chains of 7C4, 5G and 7C4 are related. Ohba *et al.* [2001]

**No.** 259

**MAb ID** 7C4

**HXB2 Location** Pol

**Author Location** RT (252–335)

**Epitope**

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade

HXB2 *HIV component:* RT

**Species (Isotype)** mouse (IgG2a)

**Ab Type** RT thumb domain

**References** Ohba *et al.* 2001; Chiba *et al.* 1997; Chiba *et al.* 1996

- 7C4: Fabs 5F and 5G both recognize the same immunodominant neutralizing RT epitope in the region of the template primer-binding site in the thumb domain recognized by MAb 7C4 – sequencing revealed the heavy chains and light chains of 7C4, 5G and 7C4 are related. Ohba *et al.* [2001]
- 7C4: 7C4 inhibits RT from HIV-1 strains IIIB, Bru, and IMS-1 but not HIV-2 strains GH-1 and LAV-2, SIV MAC, nor SIV MND. Chiba *et al.* [1997]

- 7C4: 7C4 was produced from a hybridoma cell line derived from a BALB/c mouse repeatedly immunized with RT in a vaccinia construct, and was found to inhibit RT through binding to the template primer-binding site, a possible target for RT inhibitors. Chiba *et al.* [1996]

#### IV-C-11 Vif Antibodies

- No.** 260  
**MAb ID** TG002  
**HXB2 Location** Vif (34–47)  
**Author Location** Vif (34–47)  
**Epitope** KARGWFYRHHYESP?  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Vif  
**Species (Isotype)** mouse  
**Research Contact** Transgene  
**References**
- TG002: This MAb was raised in response to a rec Vif protein derived from *E. coli*.
  - TG002: NIH AIDS Research and Reference Reagent Program: 2746.

- No.** 261  
**MAb ID** TG001  
**HXB2 Location** Vif (176–192)  
**Author Location** Vif (176–192)  
**Epitope** KPQKTKGHRGSHMTMNGH?  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Vif  
**Species (Isotype)** mouse  
**Ab Type** C-term  
**Research Contact** Transgene  
**References**
- TG001: This antibody was raised in response to a rec Vif protein derived from *E. coli*.
  - TG001: NIH AIDS Research and Reference Reagent Program: 2745.

- No.** 262  
**MAb ID** J4  
**HXB2 Location** Vif  
**Author Location** (HXB2)  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** humanized rabbit  
**References** Goncalves *et al.* 2002
- J4: The authors developed a Vif-specific intrabody single-chain FAb fragment of J4 called 14BL. When expressed intracellularly in the cytoplasm this intrabody efficiently bound Vif protein and neutralized its infectivity enhancing function. Intrabody-expressing transduced cells were highly refractory to challenge with the laboratory strain NL43 and with primary isolate strains of HIV-1. Goncalves *et al.* [2002]

- No.** 263  
**MAb ID** polyclonal  
**HXB2 Location** Vif  
**Author Location** Vif  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12  
**Species (Isotype)** mouse  
**References** Kim *et al.* 1997b
- A gag/pol, vif or CMN160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice, as well as an Ab response detected by ELISA. Kim *et al.* [1997b]

#### IV-C-12 Vpr Antibodies

- No.** 264  
**MAb ID** polyclonal  
**HXB2 Location** Vpr  
**Author Location** Vpr (89.6)  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**References** Richardson *et al.* 2003  
**Keywords** rate of progression
- Serum samples were obtained from the French GRIV (genetic resistance to HIV) cohort and tested for anti-Tat and anti-Vpr responses, as both may contribute as extracellular proteins to pathogenesis. Serum anti-Vpr IgG responses were significantly higher in stable non-progressors (CD4+ T cell counts greater than 500 cell/ul after being positive for 8 years with no ART) and unstable non-progressors (declined during a 20 month follow up), than fast progressors (CD4+ T less than 300 cells/ul within 2 years of seroconversion, some HAART). Serum anti-Tat IgG was found to be significantly higher in stable non-progressors compared to unstable non-progressors and fast progressors indicating that higher levels of serum anti-Tat IgG are associated with maintenance of non-progression status. Richardson *et al.* [2003] (**rate of progression**)

#### IV-C-13 Tat Antibodies

- No.** 265  
**MAb ID** polyclonal  
**HXB2 Location** Tat (1–15)  
**Author Location** Tat (1–15 89.6)  
**Epitope** MEPVDRPLEPWKHPG  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6, B clade HXBc2 *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** macaque (IgG)

**Ab Type** C-term, N-term, Tat basic region

**References** Silvera *et al.* 2002

**Keywords** antibody binding site definition and exposure, vaccine antigen design

- Anti-Tat and Tat toxoid responses were raised in rhesus macaques using HxBc2 and 89.6P Tat, and Tat toxoids. High anti-Tat IgG responses were observed in all animals, and helper responses were detected in 8/16, and IFN gamma CTL in 11/16. Ab and proliferative responses were observed, and the truncated 86 amino acid IIIIB Tat was more immunogenic than the full 102 amino acid Tat. Tat vaccinated animals when challenged with SHIV89.6 were infected despite a robust immune response. The most consistent reactions to the vaccinations were to peptides in regions: N-term, 1-15 (MEPVDPRLEPWKHPG), basic domain 46-60 (SYGRKKRRQR-RRAHQ), and 61-91, particularly C-term 76-90 (QPRGDPT-GPKQKKK). Silvera *et al.* [2002] (**antibody binding site definition and exposure, vaccine antigen design**)

**No.** 266

**MAb ID** polyclonal

**HXB2 Location** Tat (1–20)

**Author Location** Tat (1–20 IIIIB BH10)

**Epitope** MEPVDPRLEPWKHPGSQPKT?

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIIB *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide-2 (MALP-2)

**Species (Isotype)** mouse (IgA, IgG)

**References** Borsutzky *et al.* 2003

**Keywords** adjuvant comparison, genital and mucosal immunity, immunodominance, mucosal immunity, Th1, Th2, vaccine-induced epitopes

- Intranasal immunization of BALB/c mice Tat with MALP-2 induced stronger immune responses than i.p. vaccination of Tat with IFA. Also i.n. MALP-2 vaccination favored Th1 responses, while i.p. IFA favored Th2. Ab, T help and CTL responses were observed. MALP-2 enhanced Tat-specific IgA responses in the lung and in the genital tract. Three linear Ab epitopes were recognized. The most frequent response (80% of vaginal lavage, 100% of sera and lung lavage) was to Tat peptide 1-20. The second strongest to Tat 46-60 (20% of vaginal lavage, 50% of lung lavage, 50% of sera). Finally, 50% of the sera of Tat+ IFA i.p. immunized mice recognized Tat 73-86. Borsutzky *et al.* [2003] (**adjuvant comparison, genital and mucosal immunity, vaccine-induced epitopes, immunodominance, mucosal immunity, Th1, Th2**)

**No.** 267

**MAb ID** TA9

**HXB2 Location** Tat (1–20)

**Author Location** Tat (1–20 Lai/Bru)

**Epitope** MEPVDPRLEPWKHPGSQPKT

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse (IgG)

**Ab Type** N-term

**Research Contact** Dr. J.-L. Guesdon, Institut Pasteur, Paris

**References** Belliard *et al.* 2003

**Keywords** subtype comparisons

- This is one of 5 anti-Tat murine monoclonal antibodies generated in this study. TA9 is clade B specific, and does not recognize Tat from clade A, C, D, or CRF01 (AE). TA9 binds to the Tat peptide aa 1-61 strongly, and is also able to bind to Tat aa 1-20, and Tat peptide aa 8-53. Belliard *et al.* [2003] (**subtype comparisons**)

**No.** 268

**MAb ID** TD84

**HXB2 Location** Tat (1–20)

**Author Location** Tat (1–20 Lai/Bru)

**Epitope** MEPVDPRLEPWKHPGSQPKT

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse (IgG)

**Ab Type** N-term

**Research Contact** Dr. J.-L. Guesdon, Institut Pasteur, Paris

**References** Belliard *et al.* 2003

**Keywords** subtype comparisons

- This is one of 5 anti-Tat murine monoclonal antibodies generated in this study. TD84 is clade B specific, and does not recognize Tat from clade A, C, D, or CRF01 (AE). It reacts strongly with aa 1-61, and is able to react with aa 1-20. Belliard *et al.* [2003] (**subtype comparisons**)

**No.** 269

**MAb ID** TE135

**HXB2 Location** Tat (1–20)

**Author Location** Tat (1–20 Lai/Bru)

**Epitope** MEPVDPRLEPWKHPGSQPKT

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse (IgG)

**Ab Type** N-term

**Research Contact** Dr. J.-L. Guesdon, Institut Pasteur, Paris

**References** Belliard *et al.* 2003

**Keywords** subtype comparisons

- This is one of 5 anti-Tat murine monoclonal antibodies generated in this study. TE135 is clade B specific, and does not recognize Tat from clade A, C, D, or CRF01 (AE). It reacts strongly with aa 1-61, and is able to react with aa 1-20. Belliard *et al.* [2003] (**subtype comparisons**)

No. 270

**MAb ID** polyclonal  
**HXB2 Location** Tat (1–24)  
**Author Location** Tat (1–24)  
**Epitope** MEPVDPRLPEWKHPGSQPACTN  
**Neutralizing**  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* protein *Strain:* B clade *HIV component:* Tat *Adjuvant:* Montanide (ISA 51)  
**Species (Isotype)** human (IgG)  
**Ab Type** N-term  
**References** Noonan *et al.* 2003  
**Keywords** immunotherapy, vaccine-specific epitope characteristics

- Intramuscular injection of Tat-toxoid induced high titers of anti-Tat reactivity in serum samples of six HIV-1 positive and of four HIV negative study subjects. Anti-Tat antibodies successfully blocked extracellular Tat from transactivating HIV Tat-sensitive promoters. The anti-Tat IgG response in sera from two healthy and HIV infected patients inhibited cell entry of synthetic Tat, thus blocking its functional activity. Additionally, the anti-Tat antibodies inhibited intercellular Tat transfer as demonstrated by a co-culture cell system. All HIV-1 infected patients had Ab responses to the N-term region of Tat, and 4/4 HIV-1 + and 5/6 HIV-1 negative patients responded to the basic domain. Several additional peptides were recognized either exclusively or more commonly in the HIV+ people. The N-terminus region of Tat mediates binding to CD26, that may be involved in modulation of chemokine function, and may also mediate T-cell apoptosis. Noonan *et al.* [2003] (**vaccine-specific epitope characteristics, immunotherapy**)

No. 271

**MAb ID** NT3/2D1.1  
**HXB2 Location** Tat (2–15)  
**Author Location** Tat  
**Epitope** EPVDPNLEPWNHPS  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* Tat  
**Species (Isotype)** mouse (IgG1a)  
**Ab Type** N-term  
**References** Dingwall *et al.* 1989

- NT3/2D1.1: UK Medical Research Council AIDS reagent: ARP352.
- NT3/2D1.1: Immunoprecipitates and immunoblots HIV-1 tat protein. Dingwall *et al.* [1989]

No. 272

**MAb ID** 1.2  
**HXB2 Location** Tat (2–17)  
**Author Location** Tat (1–16)

**Epitope** EPVDPRLPEWKHPGSQ

**Neutralizing**  
**Immunogen**

**Species (Isotype)** mouse

**References** Ranki *et al.* 1995; Ovod *et al.* 1992

- 1.2: Weak expression of Tat observed in HIV+ brain tissue sample, in contrast to Nef. Ranki *et al.* [1995]

No. 273

**MAb ID** 1D9D5  
**HXB2 Location** Tat (2–21)  
**Author Location** Tat  
**Epitope** EPVDPRLPEWKHPGSQPCTA  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Tat  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** N-term

**References** Valvatne *et al.* 1996; Mhashilkar *et al.* 1995

- 1D9D5: Exogenously delivered Tat can efficiently transactivate an HIV-LTR-CAT construct in HeLa cells in the presence of 1D9D5, suggesting when considered with the results of Mhashilkar *et al.* [1995], that free Tat and not Ab bound is taken up by cells Valvatne *et al.* [1996]. Mhashilkar *et al.* [1995]; Valvatne *et al.* [1996]
- 1D9D5: Single chain antibodies, intrabodies, were engineered that can be stably expressed in the cytoplasm of mammalian cells – co-expression of an N-term intrabody can inhibit transactivation of an HIV LTR-CAT construct and block import into nucleus, but intrabody specific for exon 2 did not inhibit activity. Mhashilkar *et al.* [1995]

No. 274

**MAb ID** polyclonal  
**HXB2 Location** Tat (21–40)  
**Author Location** Tat (21–40)  
**Epitope** ACTNCYCKKCCFHCQVCFTT  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* Tat  
*Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)  
**Species (Isotype)** mouse  
**Ab Type** Tat Cys-rich domain  
**References** Devadas *et al.* 2007

**Keywords** subtype comparisons, therapeutic vaccine, vaccine-specific epitope characteristics

- Immunization of mice with a multiple -peptide conjugate system consisting of modified Tat peptides (HIV-1-Tat-MPC) induced an effective immune response. The antibodies induced against HIV-1-Tat-MPC efficiently suppressed viral replication of HIV-1 clinical isolates of subtypes A, B and F but not C. Devadas *et al.* [2007] (**therapeutic vaccine, vaccine-specific epitope characteristics, subtype comparisons**)

No. 275

**MAb ID** TB12  
**HXB2 Location** Tat (44–60)  
**Author Location** Tat (44–61 Lai/Bru)

**Epitope** GISYGRKKRRQRRPPQG  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (Isotype)** mouse (IgG)  
**Ab Type** Tat basic region  
**Research Contact** Dr. J.-L. Guesdon, Institut Pasteur, Paris  
**References** Belliard *et al.* 2003  
**Keywords** subtype comparisons

- This is one of 5 anti-Tat murine monoclonal antibodies generated in this study. TB12 is clade B and D specific, and does not recognize Tat from clade A, C, or CRF01 (AE). It reacts strongly with aa 1-61, and is also able to react with aa 44-61, in the basic region involved in Tat uptake. Belliard *et al.* [2003] (**subtype comparisons**)

No. 276

**MAb ID** polyclonal  
**HXB2 Location** Tat (46–60)  
**Author Location** Tat (46–60 IIIB BH10)  
**Epitope** SYGRKKRRQRRRAHQ?

**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide-2 (MALP-2)  
**Species (Isotype)** mouse (IgA, IgG)  
**References** Borsutzky *et al.* 2003  
**Keywords** adjuvant comparison, genital and mucosal immunity, immunodominance, mucosal immunity, Th1, Th2, vaccine-induced epitopes

- Intranasal immunization of BALB/c mice Tat with MALP-2 induced stronger immune responses than i.p. vaccination of Tat with IFA. Also i.n. MALP-2 vaccination favored Th1 responses, while i.p. IFA favored Th2. Ab, T help and CTL responses were observed. MALP-2 enhanced Tat-specific IgA responses in the lung and in the genital tract. Three linear Ab epitopes were recognized. The most frequent response (80% of vaginal lavage, 100% of sera and lung lavage) was to Tat peptide 1-20. The second strongest to Tat 46-60 (20% of vaginal lavage, 50% of lung lavage, 50% of sera). Finally, 50% of the sera of Tat+ IFA i.p. immunized mice recognized Tat 73-86. Borsutzky *et al.* [2003] (**adjuvant comparison, genital and mucosal immunity, vaccine-induced epitopes, immunodominance, mucosal immunity, Th1, Th2**)

No. 277

**MAb ID** polyclonal  
**HXB2 Location** Tat (46–60)  
**Author Location** Tat (46–60 89.6)  
**Epitope** SYGRKKRRQRRRAHQ  
**Subtype** B

**Neutralizing**  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6, B clade HXBc2 *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** macaque (IgG)  
**Ab Type** C-term, N-term, Tat basic region  
**References** Silvera *et al.* 2002  
**Keywords** antibody binding site definition and exposure, vaccine antigen design

- Anti-Tat and Tat toxoid responses were raised in rhesus macaques using HxBc2 and 89.6P Tat, and Tat toxoids. High anti-Tat IgG responses were observed in all animals, and helper responses were detected in 8/16, and IFN gamma CTL in 11/16. Ab and proliferative responses were observed, and the truncated 86 amino acid IIIB Tat was more immunogenic than the full 102 amino acid Tat. Tat vaccinated animals when challenged with SHIV89.6 were infected despite a robust immune response. The most consistent reactions to the vaccinations were to peptides in regions: N-term, 1-15 (MEPV-DRPLEPWKHPG), basic domain 46-60 (SYGRKKRRQR-RRRAHQ), and 61-91, particularly C-term 76-90 (QPRGDPT-GPKQKKK). Silvera *et al.* [2002] (**antibody binding site definition and exposure, vaccine antigen design**)

No. 278

**MAb ID** polyclonal  
**HXB2 Location** Tat (46–60)  
**Author Location** Tat (46–60 89.6)  
**Epitope** SYGRKKRRQRRRAHQ  
**Subtype** B

**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6, B clade HXBc2 *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA)  
**Species (Isotype)** macaque (IgG)  
**Ab Type** C-term, N-term, Tat basic region  
**References** Silvera *et al.* 2002  
**Keywords** antibody binding site definition and exposure, vaccine antigen design

- Anti-Tat and Tat toxoid responses were raised in rhesus macaques using HxBc2 and 89.6P Tat, and Tat toxoids. High anti-Tat IgG responses were observed in all animals, and helper responses were detected in 8/16, and IFN gamma CTL in 11/16. Ab and proliferative responses were observed, and the truncated 86 amino acid IIIB Tat was more immunogenic than the full 102 amino acid Tat. Tat vaccinated animals when challenged with SHIV89.6 were infected despite a robust immune response. The most consistent reactions to the vaccinations were to peptides in regions: N-term, 1-15 (MEPV-DRPLEPWKHPG), basic domain 46-60 (SYGRKKRRQR-RRRAHQ), and 61-91, particularly C-term 76-90 (QPRGDPT-GPKQKKK). Silvera *et al.* [2002] (**antibody binding site definition and exposure, vaccine antigen design**)

No. 279

**MAb ID** polyclonal  
**HXB2 Location** Tat (47–60)  
**Author Location** Tat (46–60)  
**Epitope** YGRKKRRQRRPPQ  
**Neutralizing**

**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* protein *Strain:* B clade *HIV component:* Tat *Adjuvant:* Montanide (ISA 51)

**Species (Isotype)** human (IgG)

**Ab Type** Tat basic region

**References** Noonan *et al.* 2003

**Keywords** immunotherapy, vaccine-specific epitope characteristics

- Intramuscular injection of Tat-toxoid induced high titers of anti-Tat reactivity in serum samples of six HIV-1 positive and of four HIV negative study subjects. Anti-Tat Abs successfully blocked extracellular Tat from transactivating HIV Tat-sensitive promoters. The anti-Tat IgG response in sera from two healthy and HIV infected patients inhibited cell entry of synthetic Tat, thus blocking its functional activity. Additionally, the anti-Tat Abs inhibited intercellular Tat transfer in a co-culture cell system. All HIV-1 infected patients had Ab responses to the N-term region of Tat, and 4/4 HIV-1 + and 5/6 HIV-1 negative patients responded to the basic domain. Several additional peptides were recognized either exclusively or more commonly in the HIV+ people. The basic region of Tat mediates binding to VEGFR2 on Kaposi's sarcoma cells and endothelial cells, and HIV patients with Kaposi's sarcoma lack Abs to this domain. Noonan *et al.* [2003] (**vaccine-specific epitope characteristics, immunotherapy**)

**No.** 280

**MAb ID** 1D2F11

**HXB2 Location** Tat (49–86)

**Author Location** Tat

**Epitope** RKKRRQRRRPPQGSQTHQVSLSKQPTSQSRGD-PTGPKE

**Neutralizing Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Tat

**Species (Isotype)** mouse (IgG1)

**Ab Type** C-term

**References** Valvatne *et al.* 1996

- 1D2F11: MAb did not bind shorter peptides – this MAb inhibited exogenously delivered Tat transactivation of an HIV-LTR-CAT construct in HeLa cells by inhibition of cellular uptake of Tat. Valvatne *et al.* [1996]

**No.** 281

**MAb ID** 2D9E7

**HXB2 Location** Tat (49–86)

**Author Location** Tat

**Epitope** RKKRRQRRRPPQGSQTHQVSLSKQPTSQSRGD-PTGPKE

**Neutralizing Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Tat

**Species (Isotype)** mouse (IgG1)

**Ab Type** C-term

**References** Valvatne *et al.* 1996

- 2D9E7: MAb did not bind shorter peptides – this MAb inhibited exogenously delivered Tat transactivation of an HIV-LTR-CAT construct in HeLa cells by inhibition of cellular uptake of Tat, but less efficiently than MAbs 1D2F11 or 4B4C4. Valvatne *et al.* [1996]

**No.** 282

**MAb ID** 4B4C4 (4B4)

**HXB2 Location** Tat (49–86)

**Author Location** Tat

**Epitope** RKKRRQRRRPPQGSQTHQVSLSKQPTSQSRGD-PTGPKE

**Neutralizing Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Tat

**Species (Isotype)** mouse (IgG1)

**Ab Type** C-term

**References** Jensen *et al.* 1997; Valvatne *et al.* 1996

- 4B4C4: MAb did not bind shorter peptides – this MAb inhibited exogenously delivered Tat transactivation of an HIV-LTR-CAT construct in HeLa cells by inhibition of cellular uptake of Tat. Valvatne *et al.* [1996]

**No.** 283

**MAb ID** 5G7D8

**HXB2 Location** Tat (49–86)

**Author Location** Tat

**Epitope** RKKRRQRRRPPQGSQTHQVSLSKQPTSQSRGD-PTGPKE

**Neutralizing Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Tat

**Species (Isotype)** mouse (IgG1)

**Ab Type** C-term

**References** Valvatne *et al.* 1996

- 5G7D8: MAb did not bind shorter peptides – this MAb inhibited exogenously delivered Tat transactivation of an HIV-LTR-CAT construct in HeLa cells by inhibition of cellular uptake of Tat, but less efficiently than 1D2F11 or 4B4C4. Valvatne *et al.* [1996]

**No.** 284

**MAb ID** polyclonal

**HXB2 Location** Tat (53–68)

**Author Location** Tat (53–68)

**Epitope** RQRRRAHQNSQTHQAS

**Subtype** B

**Neutralizing Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* Tat  
*Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** mouse

**Ab Type** Tat basic region

**References** Devadas *et al.* 2007

**Keywords** antibody generation, subtype comparisons, therapeutic vaccine

- Immunization of mice with a multipl -peptide conjugate system consisting of modified Tat peptides (HIV-1-Tat-MPC) induced an effective immune response. The antibodies induced against HIV-1-Tat-MPC efficiently suppressed viral replication of HIV-1 clinical isolates of subtypes A, B and F but not C. Devadas *et al.* [2007] (**antibody generation, therapeutic vaccine, subtype comparisons**)

**No.** 285

**MAB ID** polyclonal

**HXB2 Location** Tat (73–86)

**Author Location** Tat (73–86 IIB BH10)

**Epitope** PTSQPRGDPTGPKE?

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIB  
*HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), macrophage activating lipopeptide-2 (MALP-2)

**Species (Isotype)** mouse (IgA, IgG)

**References** Borsutzky *et al.* 2003

**Keywords** adjuvant comparison, genital and mucosal immunity, immunodominance, mucosal immunity, Th1, Th2, vaccine-induced epitopes

- Intranasal immunization of BALB/c mice Tat with MALP-2 induced stronger immune responses than i.p. vaccination of Tat with IFA. Also i.n. MALP-2 vaccination favored Th1 responses, while i.p. IFA favored Th2. Ab, T help and CTL responses were observed. MALP-2 enhanced Tat-specific IgA responses in the lung and in the genital tract. Three linear Ab epitopes were recognized. The most frequent response (80% of vaginal lavage, 100% of sera and lung lavage) was to Tat peptide 1-20. The second strongest to Tat 46-60 (20% of vaginal lavage, 50% of lung lavage, 50% of sera). Finally, 50% of the sera of Tat+ IFA i.p. immunized mice recognized Tat 73-86. Borsutzky *et al.* [2003] (**adjuvant comparison, genital and mucosal immunity, vaccine-induced epitopes, immunodominance, mucosal immunity, Th1, Th2**)

**No.** 286

**MAB ID** NT2/4D5.24

**HXB2 Location** Tat (73–86)

**Author Location** Tat

**Epitope** PTSQPRGDPTGPKE

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* Tat

**Species (Isotype)** mouse

**Ab Type** C-term

**References** Dingwall *et al.* 1989

- NT2/4D5.24: Immunoprecipitates and immunoblots HIV-1 tat protein. Dingwall *et al.* [1989]

**No.** 287

**MAB ID** polyclonal

**HXB2 Location** Tat (76–89)

**Author Location** Tat (76–90 89.6)

**Epitope** QPRGDPTGPKQKKK

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade 89.6, B clade HXBc2 *HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** macaque (IgG)

**Ab Type** C-term, N-term, Tat basic region

**References** Silvera *et al.* 2002

**Keywords** antibody binding site definition and exposure, vaccine antigen design

- Anti-Tat and Tat toxoid responses were raised in rhesus macaques using HxBc2 and 89.6P Tat, and Tat toxoids. High anti-Tat IgG responses were observed in all animals, and helper responses were detected in 8/16, and IFN gamma CTL in 11/16.. Ab and proliferative responses were observed, and the truncated 86 amino acid IIB Tat was more immunogenic than the full 102 amino acid Tat. Tat vaccinated animals when challenged with SHIV89.6 were infected despite a robust immune response. The most consistent reactions to the vaccinations were to peptides in regions: N-term, 1-15 (MEPV-DRPLEPWKHPG), basic domain 46-60 (SYGRKKRRQR-RRAHQ), and 61-91, particularly C-term 76-90 (QPRGDPT-GPKQKKK). Silvera *et al.* [2002] (**antibody binding site definition and exposure, vaccine antigen design**)

**No.** 288

**MAB ID**

**HXB2 Location** Tat

**Author Location** Tat

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIB  
*HIV component:* Tat *Adjuvant:* Incomplete Freund's Adjuvant (IFA), Montanide (ISA 51)

**Species (Isotype)** human

**References** Gringeri *et al.* 1998

**Keywords** immunotherapy

- 14 HIV-1 infected individuals were vaccinated with inactivated Tat (called Tat-toxoid), with the intent of enhancing Tat Ab levels to suppress the negative impact of secreted Tat on immune function. Tat vaccinations were safe and patients developed increased levels of Tat-specific Abs; some patients had increased Tat-specific proliferative responses. CD4 T cells tended to increase a small but significant amount after immunization, and in several patients viral load decreased. Gringeri *et al.* [1998] (**immunotherapy**)

**No.** 289

**MAB ID** L-anti-Tat

**HXB2 Location** Tat

**Author Location** Tat

**Epitope**

**Neutralizing** L P (when lipidated)

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Tat

**Species (Isotype)** mouse (IgG1)

**Research Contact** AGMED, Inc., Bedford, MA USA

**References** Cruikshank *et al.* 1997

- L-anti-Tat: Lipidated antibody can be taken up by cells and effectively block IIIB and primary virus HIV-1 replication in actively and latently infected cells. Cruikshank *et al.* [1997]

No. 290

**MAb ID** polyclonal**HXB2 Location** Tat**Author Location** Tat**Epitope****Subtype** A, B, C, CRF01\_AE, D**Neutralizing****Immunogen** HIV-1 infection**Species (Isotype)** human (IgG)**References** Belliard *et al.* 2003**Keywords** rate of progression, subtype comparisons

- Sera from 20 HIV-1 positive individuals were tested for their ability to react with Tat proteins from different clades, and were found to react with subtype A, B, and D, but not with subtype C or CRF01 (AE). Sera from 101 slow progressors and 42 fast progressors were tested for responses to Tat peptides, and compared to responses to gp41 peptide, as anti-Tat antibodies have been shown by others to be elevated in slow progressors. In this study, overall levels of Tat antibodies were not different in the two groups, however relative levels of antibodies to different Tat and gp41 peptides were observed. Belliard *et al.* [2003] (**subtype comparisons, rate of progression**)

No. 291

**MAb ID** polyclonal**HXB2 Location** Tat**Author Location** Tat**Epitope****Neutralizing** yes**Immunogen** vaccine*Vector/Type:* protein *HIV component:* Tat  
*Adjuvant:* Complete Freund's Adjuvant (CFA), red blood cells**Species (Isotype)** mouse (IgG1, IgG2a, IgG3)**References** Dominici *et al.* 2003**Keywords** adjuvant comparison, immunotherapy, Th1, Th2

- BALB/c mice were immunized intra-peritoneally with Tat protein bound to red blood cells via biotin-avidin conjugation. This antigen delivery system was successfully internalized by dendritic cells, and induced more consistent anti-Tat NAb responses and slightly increased Tat-specific CTL responses relative to Tat protein with CFA. RBC-Tat immunization induced Th1 (IgG2a) and Th2 (IgG1 and IgG3) type immune responses. Dominici *et al.* [2003] (**adjuvant comparison, immunotherapy, Th1, Th2**)

No. 292

**MAb ID** polyclonal**HXB2 Location** Tat**Author Location** Tat**Epitope****Neutralizing****Immunogen** vaccine*Vector/Type:* chitosan nanoparticles *HIV component:* Tat *Adjuvant:* adjuvant oily structure (IMS)**Species (Isotype)** mouse (IgA, IgG)**References** Le Buanec *et al.* 2001**Keywords** adjuvant comparison, mucosal immunity

- Mice were immunized with Tat toxoid (Tat detoxified by carboxamidation) either intranasally or orally using either adjuvant oily structure (IMS), nanoparticles of chitosan, or microparticles of polylactide-co-glycolide. Each of these strategies triggered IgG and IgA that inhibited Tat activity. Le Buanec *et al.* [2001] (**adjuvant comparison, mucosal immunity**)

No. 293

**MAb ID** polyclonal**HXB2 Location** Tat**Author Location** Tat (IIIB)**Epitope****Subtype** B**Neutralizing****Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* Tat *Adjuvant:* Cholera toxin (CT), E. coli mutant heat labile enterotoxin (LT-R72), E. coli heat labile enterotoxin**Species (Isotype)** mouse (IgG)**References** Marinaro *et al.* 2003**Keywords** adjuvant comparison, mucosal immunity

- Intranasal immunization of BALB/c mice with Tat and e.coli heat-labile enterotoxin (LT) and non-toxic LT-R72 LT induced strong antigen-specific IgG Abs which remained stable for one year. Tat-specific IgA responses were measured in vaginal and intestinal secretions. Immunization of BALB/c mice with native Tat (aa1-86) induced serum IgG directed against an immunodominant epitope (aa1-20) and against a second epitope (aa 46-60). CTL responses were also observed. Anti-Tat serum Abs neutralized Tat activity in a dose-independent manner. C57BL/6 remained unresponsive to Tat immunizations when Tat was co-administered with LT or cholera toxin (CT) as adjuvant; BALB/c mice are H-2d, C57BL/6 are H-2b. Congenic BALB.C mice that express H-2b rather than H-2d also could not respond to Tat, suggesting the response to Tat is constrained by the haplotype. Marinaro *et al.* [2003] (**adjuvant comparison, mucosal immunity**)

No. 294

**MAb ID** polyclonal**HXB2 Location** Tat**Author Location** Tat**Epitope****Neutralizing****Immunogen** vaccine*Vector/Type:* protein, vaccinia *Strain:* B clade MN *HIV component:* gp160, Tat  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA), polyphosphazene**Species (Isotype)** macaque (IgG)**References** Pauza *et al.* 2000



- 16 Macaques mulatta were immunized with Tat toxoid, or with Tat plus gp160, and challenged with the SHIV 89.6PD isolate. Sera from 14/16 animals neutralized Tat *in vitro*. 8 macaques developed both cellular and humoral responses to Tat, and 7/8 of these had low viral set points after rectal challenge with SHIV89.6PD. CD4+ T cells in Tat vaccinated infected animals had lower IFN-alpha and chemokine receptor expression, features of infection associated with extracellular Tat. Pauza *et al.* [2000]

No. 295

**MAb ID** polyclonal

**HXB2 Location** Tat

**Author Location** Tat

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120, Nef, Tat *Adjuvant:* AS02A (oil-in-water emulsion, 3D-monophosphoryl lipid A, QS21), AS06 (CpG, aluminum hydroxide)

**Species (Isotype)** macaque (IgG)

**References** Voss *et al.* 2003

**Keywords** adjuvant comparison, variant cross-recognition or cross-neutralization

- Monkeys were immunized with different combinations of gp120/NefTat/SIV-Tat three times over a three-month time period and intravenously challenged with SHIV 89.6P four weeks after the last immunization. Vaccination induced anti-Tat, -Nef and -gp120 Ab responses that decreased until challenge. Neutralizing Ab responses against HIV-1 MN and HIV-1 W61D were observed. Vaccination with the combination of all three proteins reduced viral load and kept animals from a CD4+ T cell decline, preventing AIDS for more than 2.5 years. The adjuvant AS02A elicited NABs and protected from disease, while AS06 did not. gp120 alone or TatNef/SIV-Tat without gp120 could not protect from disease. Voss *et al.* [2003] (**adjuvant comparison, variant cross-recognition or cross-neutralization**)

No. 296

**MAb ID** polyclonal

**HXB2 Location** Tat

**Author Location** Tat

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Zagury *et al.* 1998

**Keywords** immunotherapy, rate of progression

- Comparing 67 fast progressors with 182 non-progressors in the GRIV cohort, only anti-Tat Ab levels, not Abs to Env, Gag, or Nef, were correlated as a serological indicator of rate of progression. This suggests that raising Tat Abs may be beneficial as immunotherapy or in a vaccine. Zagury *et al.* [1998] (**immunotherapy, rate of progression**)

No. 297

**MAb ID** 2D9D5

**HXB2 Location** Tat

**Author Location** Tat

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Tat

**Species (Isotype)** mouse (IgG)

**Ab Type** C-term

**References** Mhashilkar *et al.* 1995

- 2D9D5: Single chain antibodies, intrabodies, were engineered that can be stably expressed in the cytoplasm of mammalian cells – co-expression of C-term intrabody did not inhibit trans-activation of an HIV LTR-CAT construct, in contrast to MAB 1D9D5. Mhashilkar *et al.* [1995]

No. 298

**MAb ID** polyclonal

**HXB2 Location** Tat

**Author Location** Tat (IIIB, 89.6, CMU08)

**Epitope**

**Subtype** B, CRF01\_AE

**Neutralizing**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein *Strain:* B clade *HIV component:* Tat

**Species (Isotype)** human (IgG)

**Ab Type** C-term, N-term, Tat basic region

**References** Richardson *et al.* 2003

**Keywords** antibody binding site definition and exposure, rate of progression, subtype comparisons, vaccine-specific epitope characteristics

- Serum samples were obtained from the French GRIV (genetic resistance to HIV) cohort and tested for anti-Tat and anti-Vpr responses as both may contribute as extracellular proteins to pathogenesis. Serum anti-Tat IgG responses were significantly higher and maintained for up to 20 months in stable non-progressors (CD4+ T cell counts greater than 500 cell/ul after being positive for 8 years with no ART) compared to unstable non-progressors and fast progressors (CD4+ T less than 300 cells/ul within 2 years of seroconversion, some HAART). Anti-Tat IgG from GRIV stable non-progressors recognized linear epitopes located within the N-terminal, basic and the C-terminal domains of Tat. Humoral responses of fast-progressors and of one unstable non-progressor were restricted to the basic region of Tat. Tat toxoid vaccinees from Milan tended to recognize N-terminal and C-terminal domains. Sera from some GRIV and Tat toxoid vaccinees cross-reacted in an ELISA assay with a truncated 89.6 S/HIV 89.6P Tat, 89.6P Tat, HIV-1 subtype E (CMU08) and with SIV-mac251 Tat (one sample). Richardson *et al.* [2003] (**antibody binding site definition and exposure, vaccine-specific epitope characteristics, subtype comparisons, rate of progression**)

No. 299

**MAb ID** polyclonal

**HXB2 Location** Tat

**Author Location** Tat

**Epitope**  
**Subtype** B, CRF01\_AE  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6, B clade IIIB *HIV component:* Tat  
**Species (Isotype)** macaque (IgG)  
**Ab Type** C-term, N-term, Tat basic region  
**References** Richardson *et al.* 2002  
**Keywords** antibody binding site definition and exposure, vaccine antigen design, variant cross-recognition or cross-neutralization

- Anti-Tat responses were raised in rhesus macaques using IIIB Tat, SHIV89.6P Tat, carboxymethylated Tat and 89.6P Tat toxoids. Tat IgG responses to the vaccine were cross-reactive with subtype E and MAC 251. Ab and proliferative responses were observed, and the truncated 86 amino acid IIIB Tat was more immunogenic than the full 102 amino acid Tat. Tat vaccinated animals when challenged with SHIV89.6 were infected despite a robust immune response and were not distinguishable from controls. Richardson *et al.* [2002] (**antibody binding site definition and exposure, vaccine antigen design, variant cross-recognition or cross-neutralization**)

**No.** 300  
**MAb ID** polyclonal  
**HXB2 Location** Tat  
**Author Location** Tat (IIIB, 89.6, CMU08)  
**Epitope**  
**Subtype** B, CRF01\_AE  
**Neutralizing**  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* protein *Strain:* B clade *HIV component:* Tat  
**Species (Isotype)** human (IgG)  
**Ab Type** C-term, N-term, Tat basic region  
**References** Richardson *et al.* 2003  
**Keywords** antibody binding site definition and exposure, rate of progression, subtype comparisons, vaccine-specific epitope characteristics

- Serum samples were obtained from the French GRIV (genetic resistance to HIV) cohort and tested for anti-Tat and anti-Vpr responses as both may contribute as extracellular proteins to pathogenesis. Serum anti-Tat IgG responses were significantly higher and maintained for up to 20 months in stable non-progressors (CD4+ T cell counts greater than 500 cell/ul after being positive for 8 years with no ART) compared to unstable non-progressors and fast progressors (CD4+ T less than 300 cells/ul within 2 years of seroconversion, some HAART). Anti-Tat IgG from GRIV stable non-progressors recognized linear epitopes located within the N-terminal, basic and the C-terminal domains of Tat. Humoral responses of fast-progressors and of one unstable non-progressor were restricted to the basic region of Tat. Tat toxoid vaccinees from Milan tended to recognize N-terminal and C-terminal domains. Sera from some GRIV and Tat toxoid vaccinees cross-reacted in an ELISA assay with a truncated 89.6 S/HIV 89.6P Tat, 89.6P Tat, Hiv-1 subtype E (CMU08) and with SIV-mac251 Tat (one sample). Richardson *et al.* [2003] (**antibody**

**binding site definition and exposure, vaccine-specific epitope characteristics, subtype comparisons, rate of progression)**

**No.** 301  
**MAb ID** G1  
**HXB2 Location** Tat  
**Author Location** Tat (1–15)  
**Epitope**  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** vaccine  
*Strain:* B clade *HIV component:* Tat  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** N-term  
**References** Moreau *et al.* 2004  
**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, subtype comparisons

- G1: G1 is a single-chain fragment-variable scFv antibody derived from a Tat-toxoid vaccinated uninfected volunteer. G1 binds strongly to soluble rTAT protein and to denatured rTAT, suggesting that the epitope is linear. G1 recognized HIV-1 clade B Tat proteins Bru and HXB2, but did not bind to clade E (CM240), clade C (92Br), clade D (Eli) and clade A (Ug11RP). G1 inhibited Tat-transactivation of viral replication. The VH3 heavy chains of the two phage scFvG1 VH3 heavy chain sequences of scFvG1 and scFvG2 vary (G1 CDR3, RGSTGKALDYCSPRTL; G2 CDR3, ERSQQHCN-PLLHNSGKNYAE) although both share identical Vk light chain sequences. Moreau *et al.* [2004] (**antibody binding site definition and exposure, subtype comparisons, antibody sequence variable domain**)

**No.** 302  
**MAb ID** G2  
**HXB2 Location** Tat  
**Author Location** Tat (1–15)  
**Epitope**  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** vaccine  
*Strain:* B clade *HIV component:* Tat  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** N-term  
**References** Moreau *et al.* 2004  
**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, subtype comparisons

- G2: G2 is a single-chain fragment-variable scFv antibody derived from a Tat-toxoid vaccinated uninfected volunteer. G2 binds strongly to soluble rTAT protein and to denatured rTAT, suggesting that the epitope is linear. G2 recognized HIV-1 clade B Tat proteins Bru and HXB2, but did not bind to clade E (CM240), clade C (92Br), clade D (Eli) and clade A (Ug11RP). G2 inhibited Tat-transactivation of viral replication. The VH3 heavy chains of the two phage scFvG1 VH3 heavy chain sequences of scFvG1 and scFvG2 vary (G1 CDR3, RGSTGKALDYCSPRTL; G2 CDR3, ERSQQHCN-PLLHNSGKNYAE) although both share identical Vk light

chain sequences and Tat binding sites. Moreau *et al.* [2004] (antibody binding site definition and exposure, subtype comparisons, antibody sequence variable domain)

**No.** 303  
**MAb ID** J1  
**HXB2 Location** Tat  
**Author Location** Tat (1–15)  
**Epitope**  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** vaccine  
*Strain:* B clade *HIV component:* Tat  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**Ab Type** N-term  
**References** Moreau *et al.* 2004  
**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, subtype comparisons

- J1: J1 is a single-chain fragment-variable scFv antibody derived from a Tat-toxoid vaccinated uninfected volunteer. J1 binds strongly to soluble rTAT protein and to denatured rTAT, suggesting that the epitope is linear. J1 recognized HIV-1 clade B Tat proteins Bru and HXB2, but did not bind to clade E (CM240), clade C (92Br), clade D (Eli) and clade A (Ug11RP). J1 inhibited Tat-transactivation of viral replication. Of three scFv antibodies, all bound the N-terminal amino acids 1-15, but G1 and G2 had kappa light chains and J1 had lambda, and the CDR3 of each was distinct, with J1's CDR3 sequence being: RDRYCSSPGCYKGADGGRLKDY. Moreau *et al.* [2004] (antibody binding site definition and exposure, subtype comparisons, antibody sequence variable domain)

**No.** 304  
**MAb ID** TC15  
**HXB2 Location** Tat  
**Author Location** Tat (Lai/Bru)  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Tat *Adjuvant:* Complete Freund's Adjuvant (CFA)

- Species (Isotype)** mouse (IgG)  
**Ab Type** N-term  
**Research Contact** Dr. J.-L. Guesdon, Institut Pasteur, Paris  
**References** Belliard *et al.* 2003  
**Keywords** subtype comparisons
- TC15: This is one of 5 anti-Tat murine monoclonal antibodies generated in this study. It is conformational reacting only with intact protein. It reacts with B and D clade Tat proteins, and does not recognize Tat from clade A, C, or CRF01 (AE). Belliard *et al.* [2003] (subtype comparisons)

**No.** 305  
**MAb ID** polyclonal  
**HXB2 Location** Tat  
**Author Location** Tat (Lai/Bru)

**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** SHIV infection, vaccine  
*Vector/Type:* peptide *Strain:* B clade BRU *HIV component:* Tat *Adjuvant:* aluminum phosphate, CpG immunostimulatory sequence (ISS), Montanide (ISA 720)

- Species (Isotype)** macaque (IgG)  
**Ab Type** N-term  
**References** Belliard *et al.* 2003  
**Keywords** rate of progression
- Macaques were immunized with different combinations of Tat peptides. Serum from these animals was able to inhibit Tat-induced apoptosis, and Tat antibodies are associated with long term survival. Anti-Tat antibodies generated in infected macaques tended to be restricted to the peptide 44-61, while sera from infected humans could react with several different peptides. Belliard *et al.* [2003] (rate of progression)

**No.** 306  
**MAb ID** polyclonal  
**HXB2 Location** Tat  
**Author Location** Tat (Lai/Bru)  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** SHIV infection, vaccine  
*Vector/Type:* peptide *Strain:* B clade BRU  
*HIV component:* Tat *Adjuvant:* BSA, Complete Freund's Adjuvant (CFA)

- Species (Isotype)** rabbit (IgG)  
**Ab Type** N-term  
**References** Belliard *et al.* 2003  
**Keywords** rate of progression
- 12 rabbits were immunized with different combinations of Tat peptides. Abs raised against peptide aa 8-53 did not react with the peptide 19-53, suggesting that the N-terminal region is important. Serum from these animals was able to inhibit Tat-induced apoptosis, and Tat antibodies in humans are associated with long term survival. Belliard *et al.* [2003] (rate of progression)

**No.** 307  
**MAb ID** B1E3  
**HXB2 Location** Tat  
**Author Location** Tat (44–61)  
**Epitope**  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** vaccine  
*Strain:* B clade *HIV component:* Tat

- Species (Isotype)** human (IgG1 $\kappa$ )  
**Ab Type** Tat basic region  
**References** Moreau *et al.* 2004  
**Keywords** antibody binding site definition and exposure, subtype comparisons

- B1E3: B1E3 is a MAb derived from a Tat-toxoid vaccinated uninfected volunteer. B1E3 recognized two Tat peptides, aa19-53 and aa44-61 of an unspecified HIV-1 clade B Tat protein. B1E3 demonstrates a weak binding affinity to rTAT protein in solution, suggesting that epitope recognition may be conformation dependent B1E3 did not recognize synthetic HIV-1 clade B Tat proteins Bru and HXB2, clade E (CM240), clade C (92Br), clade D (Eli) and clade A (Ug11RP). It only bound to native TAT protein, and could inhibit Tat-transactivation. Moreau *et al.* [2004] (**antibody binding site definition and exposure, subtype comparisons**)

No. 308

MAb ID J3B2

HXB2 Location Tat

Author Location Tat (44–61)

Epitope

Subtype B

Neutralizing yes

Immunogen vaccine

Strain: B clade HIV component: Tat

Species (Isotype) human (IgG1 $\lambda$ )

Ab Type Tat basic region

References Moreau *et al.* 2004

Keywords antibody binding site definition and exposure, subtype comparisons

- J3B2: J3B2 is a MAb derived from a Tat-toxoid vaccinated uninfected volunteer. B1E3 recognized two Tat peptides, aa33-37 and aa37-51 of an unspecified HIV-1 clade B Tat protein. J3B2 demonstrates a weak binding affinity to rTAT protein in solution, suggesting that epitope recognition may be conformation dependent, B1E3 did not recognize synthetic HIV-1 clade B Tat proteins Bru and HXB2, clade E (CM240), clade C (92Br), clade D (Eli) and clade A (Ug11RP). It only bound to native TAT protein, and could inhibit Tat-transactivation. Moreau *et al.* [2004] (**antibody binding site definition and exposure, subtype comparisons**)

#### IV-C-14 Rev Antibodies

No. 309

MAb ID 4G9

HXB2 Location Rev (5–15)

Author Location Rev (5–15)

Epitope SGDSDEELIRT?

Neutralizing

Immunogen vaccine

Vector/Type: protein HIV component: Rev

Species (Isotype) mouse

References Jensen *et al.* 1997

- 4G9: Mapped binding location by protein footprinting. Jensen *et al.* [1997]

No. 310

MAb ID Ab2

HXB2 Location Rev (32–50)

Author Location Rev (32–49 BRU)

Epitope EGTRQARRRRWRERQR

Neutralizing

Immunogen vaccine

Vector/Type: protein HIV component: Rev

Species (Isotype) (IgG1)

Research Contact Tony Lowe and Jonathan Karn, MRC Center, Cambridge

References Henderson &amp; Percipalle 1997

- Ab2: The Ab2 binding site overlaps the nuclear localization signal – Ab2 binding to Rev was blocked by bound HIV RNA – the cellular protein importin-beta can bind in this Arg rich region – atypically, the Rev binds specifically to importin-beta, but not to the importin-beta-importin-alpha dimer. Henderson & Percipalle [1997]

No. 311

MAb ID 10.1

HXB2 Location Rev (33–48)

Author Location Rev (33–48)

Epitope GTRQARRRRRRWRER?

Neutralizing

Immunogen

Species (Isotype)

References Maksutov *et al.* 2002; Ranki *et al.* 1995; Ranki *et al.* 1994; Ovod *et al.* 1992

- 10.1: This epitope is similar to a fragment of the human protein Complement 4 (containing C4A anaphylatoxin), GRRNRRRR. Maksutov *et al.* [2002]
- 10.1: Binds to the RRE binding site – polyclonal anti-Rev Ab detected Rev in astrocytes in 4/5 brain autopsy samples, but only one of these was positive using 10.1, suggesting most Rev was bound to RRE. Ranki *et al.* [1995]

No. 312

MAb ID 3H6

HXB2 Location Rev (38–43)

Author Location Rev (38–44)

Epitope RRNRRR

Neutralizing

Immunogen vaccine

Vector/Type: protein HIV component: Rev

Species (Isotype) mouse (IgG1 $\kappa$ )References Maksutov *et al.* 2002; Orsini *et al.* 1995

- 3H6 database comment: There is another MAb with this ID that recognizes gp41.
- 3H6: This epitope is similar to a fragment of the human protein Complement 4 (containing C4A anaphylatoxin), GRRNRRRR. Maksutov *et al.* [2002]
- 3H6: Directed against nucleolar localization/RRE binding domain – antigenic domain tentative, MAb failed to bind a RRNRRR Rev deletion mutant. Orsini *et al.* [1995]

No. 313

MAb ID 8E7

HXB2 Location Rev (70–84)

Author Location Rev (70–84)

Epitope PVPLQLPPLERLTLTD

Neutralizing

Immunogen vaccine

Vector/Type: protein HIV component: Rev

Species (Isotype) mouse (IgG2a $\kappa$ )

**References** Maksiotov *et al.* 2002; Boe *et al.* 1998; Jensen *et al.* 1997; Szilvay *et al.* 1995; Kalland *et al.* 1994b; Kalland *et al.* 1994a

- 8E7: This epitope is similar fragments of the human protein Epidermal growth factor receptor substrate 15, EPVPM-SLPPA, and Insulin-like growth factor binding protein complex acid labile chain precursor, QPPGLERLWLEGN-PWDCG. Maksiotov *et al.* [2002]
- 8E7: HIV-1 RNA and Rev localize to the same region in the nucleoplasm, but the splicing factor SC-35 localizes in different speckles with the nucleoplasm than Rev – intron containing beta-globin was distributed similarly to HIV-1, suggesting Rev and HIV-1 RNAs interact at putative sites of mRNA transcriptions and splicing. Boe *et al.* [1998]
- 8E7: Peptide interaction mapped to aa 70-84, 75-88 – protein footprint to 65-88. Jensen *et al.* [1997]
- 8E7: 8E7 worked in indirect immunofluorescence and also detected Rev in WB assays – used to detect localization of Rev in several compartments including the nucleoli, nucleoplasm, perinuclear zone, and cytoplasm – Rev co-localized with host cell factors known to assemble on nascent transcripts – Rev shuttles continuously between cytoplasmic and nucleoplasmic compartments. Kalland *et al.* [1994a,b]; Szilvay *et al.* [1995]

**No.** 314

**MAb ID** 9G2 (9G2G4D6E8)

**HXB2 Location** Rev (70–84)

**Author Location** Rev (70–84)

**Epitope** PVPLQLPLLERLTLD

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Rev

**Species (Isotype)** mouse (IgG2 $\kappa$ )

**Research Contact** Anne Marie Szilvay

**References** Maksiotov *et al.* 2002; Jensen *et al.* 1997; Kalland *et al.* 1994a

- 9G2: Called 9G2G4D6E8: UK Medical Research Council AIDS reagent: ARP3058.
- 9G2: This epitope is similar fragments of the human protein Epidermal growth factor receptor substrate 15, EPVPM-SLPPA, and Insulin-like growth factor binding protein complex acid labile chain precursor, QPPGLERLWLEGN-PWDCG. Maksiotov *et al.* [2002]
- 9G2: Peptide interaction mapped to aa 70-84, 75-88 – protein footprint to 65-88. Jensen *et al.* [1997]
- 9G2: Worked in indirect immunofluorescence and also detected Rev in WB assays – used to detect localization of Rev throughout the cell. Kalland *et al.* [1994a]

**No.** 315

**MAb ID** Ab4

**HXB2 Location** Rev (72–91)

**Author Location** Rev (72–91 BRU)

**Epitope** PLQLPLLERLTLDNCNEDCGT

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Rev

**Species (Isotype)** (IgG1)

**Research Contact** Tony Lowe and Jonathan Karn, MRC Center, Cambridge

**References** Maksiotov *et al.* 2002; Henderson & Percipalle 1997

- Ab4: This epitope is similar fragments of the human protein Epidermal growth factor receptor substrate 15, EPVPM-SLPPA, and Insulin-like growth factor binding protein complex acid labile chain precursor, QPPGLERLWLEGN-PWDCG. Maksiotov *et al.* [2002]
- Ab4: The binding site overlaps the nuclear export signal – binding was not blocked by bound HIV RNA and may be accessible for protein interaction. Henderson & Percipalle [1997]

**No.** 316

**MAb ID** 3G4

**HXB2 Location** Rev (90–116)

**Author Location** Rev (90–116)

**Epitope** GTSGTQGVGSPQILVESPTVLESGETKE?

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Rev

**Species (Isotype)** mouse (IgG1 $\kappa$ )

**References** Orsini *et al.* 1995

- 3G4: Binds to a region that can be dispensed with and still retain Rev function. Orsini *et al.* [1995]

**No.** 317

**MAb ID** 1G10 (IG10F4)

**HXB2 Location** Rev (96–105)

**Author Location** Rev (95–105)

**Epitope** GVGSPQILVE

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Rev

**Species (Isotype)** mouse (IgG2b $\kappa$ )

**Research Contact** Anne Marie Szilvay

**References** Jensen *et al.* 1997; Kalland *et al.* 1994a

- 1G10: Called IG10F4: UK Medical Research Council AIDS reagent: ARP3060.
- 1G10: Peptide interaction mapped to aa 91-105, 96-110 – protein footprint to aa 10-20, and 95-105. Jensen *et al.* [1997]
- 1G10: Bound Rev in indirect immunofluorescence and also detected Rev in WB – used to detect localization of Rev throughout the cell. Kalland *et al.* [1994a]

**No.** 318

**MAb ID** 1G7

**HXB2 Location** Rev (96–105)

**Author Location** Rev (95–105)

**Epitope** GVGSPQILVE

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Rev

**Species (Isotype)** mouse (IgG2b $\kappa$ )

**References** Jensen *et al.* 1997; Kalland *et al.* 1994a

- 1G7: Peptide interaction mapped to aa 91-105, 96-110 – protein footprint to aa 95-105. Jensen *et al.* [1997]
- 1G7: Worked in indirect immunofluorescence and also detected Rev in WB – used to detect localization of Rev throughout the cell. Kalland *et al.* [1994a]

No. 319  
**MAb ID** Ab3  
**HXB2 Location** Rev (102–116)  
**Author Location** Rev (102–116 BRU)  
**Epitope** ILVESPTVLES DKTE  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Rev  
**Species (Isotype)** (IgG1)  
**Research Contact** Tony Lowe and Jonathan Karn, MRC, Cambridge  
**References** Henderson & Percipalle 1997  
 • Ab3: This binding site is at the carboxy end of Rev – Ab3 binding was not blocked by bound HIV RNA. Henderson & Percipalle [1997]

No. 320  
**MAb ID** 2G2  
**HXB2 Location** Rev  
**Author Location** Rev  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Rev  
**Species (Isotype)** mouse (IgG1κ)  
**References** Orsini *et al.* 1995  
 • 2G2: Does not bind to any of a set of glutathione S-transferase (GST) Rev fusion proteins, or to Rev in a RIPA buffer, suggesting a conformational epitope. Orsini *et al.* [1995]

#### IV-C-15 Vpu Antibodies

No. 321  
**MAb ID** DE7  
**HXB2 Location** Vpu (42–63)  
**Author Location** Vpu (41–62)  
**Epitope** LIDRLIERAEDSGNESEGEISA  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* Vpu  
*Adjuvant:* BSA  
**Species (Isotype)** mouse (IgG1)  
**References** Gharbi-Benarous *et al.* 2004  
**Keywords** antibody binding site definition and exposure, antibody generation  
 • DE7: This MAb was generated against the phosphorylated Vpu41-62 peptide. Phosphorylation of Vpu, at the Serines of the DSGXXS motif, is required for interaction of Vpu with the ubiquitin ligase that triggers CD4 degradation and infectious virion release. DE7 bound peptide conformation was analyzed using STD NMR epitope mapping, TRNOESY conformational analysis and molecular dynamics simulation, and found to adopt a compact structure with several bends, including a tight bend at DpSGNEpS. Gharbi-Benarous *et al.* [2004] (**antibody binding site definition and exposure, antibody generation**)

#### IV-C-16 gp160 Antibodies

No. 322  
**MAb ID** M85  
**HXB2 Location** gp160 (30–51)  
**Author Location** gp120 (30–51 LAI)  
**Epitope** ATEKLWVTVYYGVPVWKEATTT  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C1  
**Research Contact** Fulvia di Marzo Veronese  
**References** Koefoed *et al.* 2005; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992

**Keywords** antibody binding site definition and exposure  
 • M85: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. M85 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, and has a linear C1 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)  
 • M85: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding. Wyatt *et al.* [1997]  
 • M85: Binding inhibited by MAb 4D4#85, enhanced by conformationally sensitive anti-V3 MAb 5G11, and some anti-18 MAbs. Moore & Sodroski [1996]  
 • M85: C1 domain – mutation 40 Y/D impairs binding – the relative affinity for denatured/native gp120 is < .01, suggesting conformational component. Moore *et al.* [1994c]  
 • M85: Immunoblot and RIP reactive for strains IIIB, 451, MN, RF, and RUTZ – binds deglycosylated gp120. di Marzo Veronese *et al.* [1992]

No. 323  
**MAb ID** 7E2/4  
**HXB2 Location** gp160 (31–50)  
**Author Location** gp120 (31–50 LAI)  
**Epitope** TEKLWVTVYYGVPVWKEATT  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**Research Contact** S. Ranjbar, NIBSC, UK  
**References** Maksutov *et al.* 2002; Moore *et al.* 1994c  
 • 7E2/4: UK Medical Research Council AIDS reagent: ARP3050.  
 • 7E2/4: This epitope has a high degree of similarity with the platelet membrane glycoprotein IIIA precursor (GLIIIA) (integrin beta- 3) (CD61): PLYKEATSTF. Maksutov *et al.* [2002]

- 7E2/4: C1 domain – the relative affinity for denatured/native gp120 is .07, suggesting conformational component. Moore *et al.* [1994c]

No. 324

**MAb ID** 4D4#85

**HXB2 Location** gp160 (41–50)

**Author Location** gp120 (LAI)

**Epitope** GVPVWKEATT

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Strain:* B clade LAI *HIV component:* Env

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 C1

**Research Contact** S. Nigida and L. Arthur, NCI, Frederick, MD USA

**References** Maksiotov *et al.* 2002; Binley *et al.* 1998; Wyatt *et al.* 1997; Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c

- 4D4#85: This epitope has a high degree of similarity with the platelet membrane glycoprotein IIIA precursor (GLIIIA) (integrin beta- 3) (CD61): PLYKEATSTF. Maksiotov *et al.* [2002]
- 4D4#85: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein ( Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 4D4#85: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-50, are deleted. Wyatt *et al.* [1997]
- 4D4#85: Inhibits binding of C1 MAb M85, C1-C5 discontinuous epitope MAbs 181 and 212A, and CD4 binding induced MAbs 48d and 17b. Moore & Sodroski [1996]
- 4D4#85: C1 domain – the relative affinity, denatured/native gp120 is 0.1 – mutation 45 W/S impairs binding. Moore *et al.* [1994c]

No. 325

**MAb ID** M92

**HXB2 Location** gp160 (41–50)

**Author Location** gp120 (31–50 LAI)

**Epitope** GVPVWKEATT

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Env

**Species (Isotype)** rat (IgG1)

**Ab Type** gp120 C1

**Research Contact** Fulvia di Marzo Veronese

**References** Maksiotov *et al.* 2002; Moore *et al.* 1994d; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992

- M92: This epitope has a high degree of similarity with the platelet membrane glycoprotein IIIA precursor (GLIIIA) (integrin beta- 3) (CD61): PLYKEATSTF. Maksiotov *et al.* [2002]
- M92: The relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]
- M92: Immunoblot reactive, RIP negative, but precipitates deglycosylated gp120 – reacts with strains IIIB, 451, MN, RF, and RUTZ. di Marzo Veronese *et al.* [1992]

No. 326

**MAb ID** M86

**HXB2 Location** gp160 (42–61)

**Author Location** gp120 (42–61 LAI)

**Epitope** VPVWKEATTTLFCASDAKAY

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Env

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C1

**Research Contact** Fulvia di Marzo Veronese

**References** Maksiotov *et al.* 2002; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992

- M86: This epitope has a high degree of similarity with the platelet membrane glycoprotein IIIA precursor (GLIIIA) (integrin beta- 3) (CD61): PLYKEATSTF. Maksiotov *et al.* [2002]
- M86: C1 domain – the relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]
- M86: Immunoblot and RIP reactive for strains IIIB, 451, MN, RF, and RUTZ – binds deglycosylated gp120. di Marzo Veronese *et al.* [1992]

No. 327

**MAb ID** polyclonal

**HXB2 Location** gp160 (52–71)

**Author Location** Env (42–61 LAI)

**Epitope** LFCASDAKAYDTEVHNVWAT

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* vaccinia *HIV component:* Env

**Species (Isotype)** mouse

**Ab Type** gp120 C1

**References** Collado *et al.* 2000

- Vaccinia p14 can elicit NABs and p39 tends to be immunodominant, so these two proteins were fused to regions of HIV-1 Env – reduced glycosylation was noted when p14 or p39 was placed in the N-term region of the fusion protein – chimeric proteins shifted the Env Ab response from V3 to either a C1 or C4 domain, depending on the construct – all chimeric Env proteins: 14kEnv, 39kEnv, and Env39k elicited a strong Ab response to the C1 region of gp120 (LFCASDAKAYDTEVHNVWAT), and Env39k mounted a strong response to the C4 region (KAMYAPPISGQIRCSSNITG) Collado *et al.* [2000]

No. 328

**MAb ID** 133/237  
**HXB2 Location** gp160 (61–70)  
**Author Location** gp120 (51–70 LAI)  
**Epitope** YDTEVHNVWA  
**Subtype** B  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C1  
**References** Pantophlet *et al.* 2004; Moore *et al.* 1994d; Moore *et al.* 1994c; Niedrig *et al.* 1992b

**Keywords** vaccine antigen design

- 133/237: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 133/237. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 133/237: The relative affinity, denatured/native gp120 is 1.4 – mutation of position 69 W/L impairs binding. Moore *et al.* [1994c]
- 133/237: Region of overlap for reactive peptides is WATHA – weak neutralization of lab strains. Niedrig *et al.* [1992b]

**No.** 329

**MAb ID** 133/290  
**HXB2 Location** gp160 (61–70)  
**Author Location** gp120 (61–70 LAI)  
**Epitope** YDTEVHNVWA  
**Subtype** B  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C1  
**Research Contact** M. Niedrig  
**References** Pantophlet *et al.* 2003b; Yang *et al.* 2000; Binley *et al.* 1998; Wyatt *et al.* 1997; Binley *et al.* 1997a; Moore & Sodroski 1996; Wyatt *et al.* 1995; Moore *et al.* 1994d; Moore *et al.* 1994c; Thali *et al.* 1993; Niedrig *et al.* 1992b

**Keywords** vaccine antigen design

- 133/290: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)

- 133/290: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- 133/290: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 133/290: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding. Wyatt *et al.* [1997]
- 133/290: Reciprocal binding inhibition with the antibody 522-149, that binds to a discontinuous epitope – binding is enhanced by some C5 and C1 binding site antibodies. Moore & Sodroski [1996]
- 133/290: Used for antigen capture assay, either to bind gp120 to the ELISA plate, or to quantify bound gp120. Wyatt *et al.* [1995]
- 133/290: The relative affinity for denatured/native gp120 is 2.2 – mutation in position 69 W/L impairs binding. Moore *et al.* [1994c]
- 133/290: Region of overlap for reactive peptides is WATHA – weak neutralization of lab strains. Niedrig *et al.* [1992b]

**No.** 330

**MAb ID** 133/11  
**HXB2 Location** gp160 (64–78)  
**Author Location** gp120 (64–78)  
**Epitope** EVHNVWATHACVPTD  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C1  
**References** Niedrig *et al.* 1992b

- 133/11: Region of overlap for reactive peptides is WATHA – weak neutralization of lab strains. Niedrig *et al.* [1992b]

**No.** 331

**MAb ID** D/3G5  
**HXB2 Location** gp160 (73–82)  
**Author Location** gp120 (73–82 LAI)  
**Epitope** ACVPTDPNPQ  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG1)



**Ab Type** gp120 C1  
**References** Bristow *et al.* 1994  
 • D/3G5: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

**No.** 332  
**MAb ID** D/6A11  
**HXB2 Location** gp160 (73–82)  
**Author Location** gp120 (73–82 LAI)  
**Epitope** ACVPTDPNPQ  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 C1  
**References** Bristow *et al.* 1994  
 • D/6A11: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

**No.** 333  
**MAb ID** D/5E12  
**HXB2 Location** gp160 (73–92)  
**Author Location** gp120 (73–92 LAI)  
**Epitope** ACVPTDPNPQEVVLVNVTEN  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 C1  
**References** Bristow *et al.* 1994  
 • D/5E12: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

**No.** 334  
**MAb ID** L5.1  
**HXB2 Location** gp160 (79–93)  
**Author Location** gp120 (89–103 IIIB)  
**Epitope** PNPQEVVLVNVTENF  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**References** Akerblom *et al.* 1990

**No.** 335  
**MAb ID** 4A7C6  
**HXB2 Location** gp160 (81–90)  
**Author Location** gp120 (81–90 LAI)  
**Epitope** PQEVVLVNVT  
**Subtype** B  
**Neutralizing**

**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**Research Contact** R. Tedder  
**References** Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; Moore & Ho 1993; Thali *et al.* 1993; Thiriart *et al.* 1989  
 • 4A7C6: UK Medical Research Council AIDS reagent: ARP 360.  
 • 4A7C6: Reciprocal binding inhibition with the antibody 133/192 – enhanced by anti-C5 antibodies, and C1 antibody 135/9. Moore & Sodroski [1996]  
 • 4A7C6: The relative affinity for denatured/native gp120 is 7.9 – mutation 88 N/P impairs binding. Moore *et al.* [1994c]  
 • 4A7C6: C1 region epitope (88 N/P substitutions abrogates binding), but substitutions 380 G/F and 420 I/R also impaired binding. Moore *et al.* [1994d]  
 • 4A7C6: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

**No.** 336  
**MAb ID** 1D10  
**HXB2 Location** gp160 (81–100)  
**Author Location** gp120 (81–100 LAI)  
**Epitope** PQEVVLVNVTENFDMWKNDM  
**Subtype** B  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120  
**Species (Isotype)** rat  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Nakamura *et al.* 1992; Berman *et al.* 1991; Dowbenko *et al.* 1988  
 • 1D10: The relative affinity for denatured/native gp120 is 13 – mutation 88 N/P impairs binding. Moore *et al.* [1994c]  
 • 1D10: Cross-blocks 5B3 in IIIB-rsgp160 ELISA – type specific in rgp120 ELISA binding. Nakamura *et al.* [1992]

**No.** 337  
**MAb ID** B242  
**HXB2 Location** gp160 (83–92)  
**Author Location** gp120 (83–92 LAI)  
**Epitope** EVVLVNVTEN  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C1  
**References** Bristow *et al.* 1994  
 • B242: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp160 IIIB:NL43, MicroGenSys. Bristow *et al.* [1994]

**No.** 338  
**MAb ID** 133/192  
**HXB2 Location** gp160 (91–100)

**Author Location** gp120 (91–100 LAI)**Epitope** ENFDMWKNDM**Subtype** B**Neutralizing** L**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade IIIB*HIV component:* gp120**Species (Isotype)** mouse (IgG1)**Ab Type** gp120 C1**Research Contact** Matthias Niedrig**References** Pantophlet *et al.* 2004; Pantophlet *et al.* 2003b; Binley *et al.* 1998; Binley *et al.* 1997a; Trkola *et al.* 1996a; Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; Moore *et al.* 1993b; Niedrig *et al.* 1992b**Keywords** vaccine antigen design

- 133/192: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 133/192. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 133/192: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 133/192: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 133/192: Reciprocal binding inhibition with the antibody 4A7C6 – enhanced by some anti-C5 and-C1 antibodies. Moore & Sodroski [1996]
- 133/192: Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- 133/192: The relative affinity for denatured/native gp120 is 1.8. Moore *et al.* [1994c]
- 133/192: C1 region – substitutions 76P/Y, 113 D/A or R, 117 K/W, 420 I/R, 427 W/S impair binding, other substitutions enhanced binding. Moore *et al.* [1994d]
- 133/192: Epitope seems complex, binds multiple peptides – weak neutralization of lab strain. Niedrig *et al.* [1992b]

**No.** 339**MAb ID** 489.1(961)**HXB2 Location** gp160 (91–100)**Author Location** gp120 (91–100 LAI)**Epitope** ENFDMWKNDM**Subtype** B**Neutralizing****Immunogen** vaccine*Strain:* B clade LAI *HIV component:* Env**Species (Isotype)** mouse (IgG)**Ab Type** gp120 C1**Research Contact** C. Bruck, SKB, Belgium**References** Moore *et al.* 1994c

- 489.1(961): NIH AIDS Research and Reference Reagent Program: 961.
- 489.1(961): The relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]

**No.** 340**MAb ID** 5B3**HXB2 Location** gp160 (91–100)**Author Location** gp120 (91–100 LAI)**Epitope** ENFDMWKNDM**Subtype** B**Neutralizing** no**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade IIIB*HIV component:* gp160**Species (Isotype)** mouse (IgG)**Ab Type** gp120 C1**References** Moore *et al.* 1994c; Beretta & Dalgleish 1994; Nakamura *et al.* 1992; Berman *et al.* 1991

- 5B3: The relative affinity of denatured/native gp120 is 8.3. Moore *et al.* [1994c]
- 5B3: Cross-blocks 1D10 in competitive IIIB-rsgp160 ELISA – no neutralization – blocks IIIB-gp120 sCD4 binding – localized binding to residues 72-106. Nakamura *et al.* [1992]
- 5B3: Blocks gp120 -CD4 binding. Berman *et al.* [1991]

**No.** 341**MAb ID** B10**HXB2 Location** gp160 (91–100)**Author Location** gp120 (91–100 LAI)**Epitope** ENFDMWKNDM**Subtype** B**Neutralizing****Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade LAI*HIV component:* gp160**Species (Isotype)** mouse (IgG1)**Ab Type** gp120 C1**References** Moore *et al.* 1994c; Abacioglu *et al.* 1994

- B10: There is FNM/FDM polymorphism in LAI-based peptides, and N is essential (J. P. Moore, per. comm.)
- B10: C1 region – epitope boundaries mapped by peptide scanning, FNMW core. Abacioglu *et al.* [1994]
- B10: The relative affinity for denatured/native gp120 is 0.4. Moore *et al.* [1994c]

**No.** 342**MAb ID** B2**HXB2 Location** gp160 (91–100)**Author Location** gp120 (91–100 LAI)

**Epitope** ENFDMWKNDM  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG2b)  
**Ab Type** gp120 C1  
**References** Binley *et al.* 1997a; Moore *et al.* 1994d; Moore *et al.* 1994c; Abacioglu *et al.* 1994; Thali *et al.* 1993

- B2: There is FNM/FDM polymorphism in LAI-based peptides, and N is essential (J. P. Moore, per. comm.)
- B2: C1 region – epitope boundaries mapped by peptide scanning, FNMW core. Abacioglu *et al.* [1994]
- B2: The relative affinity for denatured/native gp120 is 1.4. Moore *et al.* [1994c]

**No.** 343  
**MAB ID** C6 (Ch6)  
**HXB2 Location** gp160 (91–100)  
**Author Location** gp120 (91–100 LAI)  
**Epitope** ENFDMWKNDM  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C1  
**References** Pincus *et al.* 1996; Moore *et al.* 1994c; Abacioglu *et al.* 1994; Pincus & McClure 1993

- C6: There is FNM/FDM polymorphism in LAI-based peptides – N is essential (J. P. Moore, per. comm.)
- C6: NIH AIDS Research and Reference Reagent Program: 810.
- C6: Called Ch6 – binds to gp120 but not to infected cells – when linked to ricin A, the immunotoxin did not mediate cell killing – sCD4 has no effect. Pincus & McClure [1993]; Pincus *et al.* [1996]
- C6: C1 region – epitope boundaries mapped by peptide scanning, FNMW core. Abacioglu *et al.* [1994]
- C6: The relative affinity for denatured/native gp120 is 0.9. Moore *et al.* [1994c]

**No.** 344  
**MAB ID** MF49.1  
**HXB2 Location** gp160 (91–100)  
**Author Location** gp120 (91–100 LAI)  
**Epitope** ENFDMWKNDM  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF49.1: The relative affinity of denatured/native gp120 is 3.8. Moore *et al.* [1994c]

**No.** 345  
**MAB ID** T1.1  
**HXB2 Location** gp160 (91–100)  
**Author Location** gp120 (91–100 LAI)  
**Epitope** ENFDMWKNDM  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *HIV component:* gp160  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Broliden *et al.* 1990; Akerblom *et al.* 1990

- T1.1: C1 region – the relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]
- T1.1: Also reacted in solid phase with gp120(234–248) NGT-GPCTNVSTQCT. Akerblom *et al.* [1990]
- T1.1: No ADCC activity – reactive peptide: NVTENFN-MWKNDMVEQ, IIIB. Broliden *et al.* [1990]

**No.** 346  
**MAB ID** T7.1  
**HXB2 Location** gp160 (91–100)  
**Author Location** gp120 (91–100 LAI)  
**Epitope** ENFDMWKNDM  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994d; Moore *et al.* 1994c; Bolmstedt *et al.* 1990; Akerblom *et al.* 1990

- T7.1: The relative affinity of denatured/native gp120 is 4.0. Moore *et al.* [1994c]

**No.** 347  
**MAB ID** T9  
**HXB2 Location** gp160 (91–100)  
**Author Location** gp120 (91–100 LAI)  
**Epitope** ENFDMWKNDM  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**Research Contact** Lennart Akerblom, Britta Wahren and Jorma Hinkula  
**References** Binley *et al.* 1997a; Moore *et al.* 1994d; Moore *et al.* 1994c; Bolmstedt *et al.* 1990; Akerblom *et al.* 1990

- T9 database comment: There are two HIV-Abs with the name T9, one binds to gp41, one to gp120.
- T9: The relative affinity of denatured/native gp120 is 7.9. Moore *et al.* [1994c]

- T9: Binds to the C1 region – 45 W/S, 88 N/P, 256 S/Y, 262 N/T, 475 M/S, 485 1.83, and 491 I/F enhanced binding, no substitution tested significantly inhibited. Moore *et al.* [1994d]

No. 348

**MAb ID** GV4D3

**HXB2 Location** gp160 (92–100)

**Author Location** gp120 (92–100 IIIB)

**Epitope** NFNMMWKNDM

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein-Ab complex *HIV component:* gp120-Mab complex

**Species (Isotype)** mouse

**Ab Type** gp120 C1

**Research Contact** Patricia Earl and Christopher Broder, NIH

**References** Denisova *et al.* 1996

- GV4D3: When anti-V3 MAb M77 was bound to gp120 and used as an immunogen, it stimulated many MAbs to linear epitopes – MAbs GV4H4 and GV5F9 are homologous to GV4D3 and were generated in the same experiment. Denisova *et al.* [1996]

No. 349

**MAb ID** B27

**HXB2 Location** gp160 (93–96)

**Author Location** gp120 (94–97 BH10)

**Epitope** FNMM

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C1

**References** Bristow *et al.* 1994; Abacioglu *et al.* 1994

- B27: C1 region – epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]
- B27: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp160 IIIB:NL43, MicroGenSys. Bristow *et al.* [1994]

No. 350

**MAb ID** B9

**HXB2 Location** gp160 (93–96)

**Author Location** gp120 (93–96 LAI)

**Epitope** FNMM

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C1

**References** Abacioglu *et al.* 1994

- B9: Binds C1 region – epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 351

**MAb ID** B35

**HXB2 Location** gp160 (93–98)

**Author Location** gp120 (94–99 BH10)

**Epitope** FNMWKN

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C1

**References** Abacioglu *et al.* 1994

- B35: C1 region – epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 352

**MAb ID** D/4B5

**HXB2 Location** gp160 (93–101)

**Author Location** gp120 (93–101 LAI)

**Epitope** FNMWKNDMV

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp120

**Species (Isotype)** mouse

**Ab Type** gp120 C1

**References** Bristow *et al.* 1994

- D/4B5: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

No. 353

**MAb ID** D/5A11

**HXB2 Location** gp160 (93–101)

**Author Location** gp120 (93–101 LAI)

**Epitope** FNMWKNDMV

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp120

**Species (Isotype)** mouse

**Ab Type** gp120 C1

**References** Bristow *et al.* 1994

- D/5A11: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

No. 354

**MAb ID** D/6B2

**HXB2 Location** gp160 (93–101)

**Author Location** gp120 (93–101 LAI)

**Epitope** FNMWKNDMV

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C1

**References** Bristow *et al.* 1994

- D/6B2: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

**No.** 355  
**MAb ID** B18  
**HXB2 Location** gp160 (101–110)  
**Author Location** gp120 (101–110 LAI)  
**Epitope** VEQMHEDIIS  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG2a)  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Abacioglu *et al.* 1994

- B18: C1 region – epitope boundaries mapped by peptide scanning, HEDII core. Abacioglu *et al.* [1994]
- B18: The relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]

**No.** 356  
**MAb ID** B20  
**HXB2 Location** gp160 (101–110)  
**Author Location** gp120 (101–110 LAI)  
**Epitope** VEQMHEDIIS  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG2a)  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Abacioglu *et al.* 1994

- B20: C1 region – epitope boundaries mapped by peptide scanning – HEDII core. Abacioglu *et al.* [1994]
- B20: The relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]

**No.** 357  
**MAb ID** MF39.1 (39.1)  
**HXB2 Location** gp160 (101–110)  
**Author Location** gp120 (101–110 LAI)  
**Epitope** VEQMHEDIIS  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Cook *et al.* 1994; Thiriart *et al.* 1989

- MF39.1: Called 39.1, and is probably the same as MF39.1 – MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]

- MF39.1: The relative affinity of denatured/native gp120 is 30. Moore *et al.* [1994c]

**No.** 358  
**MAb ID** 187.2.1 (187.1)  
**HXB2 Location** gp160 (101–120)  
**Author Location** gp120 (101–120 LAI)  
**Epitope** VEQMHEDIISLWDQSLKPCV  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**Research Contact** Claudine Bruck and Clothilde Thiriart  
**References** Moore *et al.* 1994d; Moore *et al.* 1994c; Cook *et al.* 1994; Moore & Ho 1993; Thiriart *et al.* 1989

- 187.2.1: UK Medical Research Council AIDS reagent: ARP332.
- 187.2.1: Called 187.1, and is probably the same as 187.2.1 – MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]
- 187.2.1: The relative affinity for denatured/native gp120 is 7 – mutations 113 D/A (not D/R) and 117 K/W impair binding. Moore *et al.* [1994c]
- 187.2.1: Called 187.1, and is probably the same as 187.2.1 – bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

**No.** 359  
**MAb ID** 37.1.1(ARP 327) (37.1)  
**HXB2 Location** gp160 (101–120)  
**Author Location** gp120 (101–120 LAI)  
**Epitope** VEQMHEDIISLWDQSLKPCV  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**Research Contact** Claudine Bruck  
**References** Moore *et al.* 1994c; Moore & Ho 1993; Thiriart *et al.* 1989

- 37.1.1: UK Medical Research Council AIDS reagent: ARP327.
- 37.1.1: The relative affinity for denatured/native gp120 is 8.6 – mutations 113 D/R (not D/A) and 117 K/W impair binding. Moore *et al.* [1994c]
- 37.1.1: Called 37.1 – bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

**No.** 360  
**MAb ID** 6D8  
**HXB2 Location** gp160 (101–120)  
**Author Location** gp120 (101–120 LAI)  
**Epitope** VEQMHEDIISLWDQSLKPCV

- Subtype B**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120
- Species (Isotype)** rat  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Nakamura *et al.* 1992; Dowbenko *et al.* 1988
- 6D8: The relative affinity for denatured/native gp120 is 15 – mutations 113 D/R and 113 D/A impair binding. Moore *et al.* [1994c]
  - 6D8: Highly cross reactive with multiple stains by rgp120 ELISA. Nakamura *et al.* [1992]
- No.** 361  
**MAb ID** M96  
**HXB2 Location** gp160 (101–120)  
**Author Location** gp120 (101–120 LAI)  
**Epitope** VEQMHEDIISLWDQSLKPCV  
**Subtype B**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env
- Species (Isotype)** rat (IgG2a)  
**Ab Type** gp120 C1  
**Research Contact** Fulvia di Marzo Veronese  
**References** Moore *et al.* 1994d; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992
- M96: C1 region – the relative affinity for denatured/native gp120 is 6. Moore *et al.* [1994c]
  - M96: Immunoblot reactive for strains IIIB, 451, MN, RF, and RUTZ. di Marzo Veronese *et al.* [1992]
- No.** 362  
**MAb ID** MF119.1  
**HXB2 Location** gp160 (101–120)  
**Author Location** gp120 (101–120 LAI)  
**Epitope** VEQMHEDIISLWDQSLKPCV  
**Subtype B**  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env
- Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Thiriart *et al.* 1989
- MF119.1: The relative affinity for denatured/native gp120 is 30 – mutations 113 D/A, 113 D/R, and 117 K/W impair binding. Moore *et al.* [1994c]
- No.** 363  
**MAb ID** MF4.1  
**HXB2 Location** gp160 (101–120)  
**Author Location** gp120 (101–120 LAI)  
**Epitope** VEQMHEDIISLWDQSLKPCV  
**Subtype B**  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env
- Species (Isotype)** mouse (IgG)
- Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Thiriart *et al.* 1989
- MF4.1: The relative affinity for denatured/native gp120 is 8. Moore *et al.* [1994c]
- No.** 364  
**MAb ID** MF53.1  
**HXB2 Location** gp160 (101–120)  
**Author Location** gp120 (101–120 LAI)  
**Epitope** VEQMHEDIISLWDQSLKPCV  
**Subtype B**  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env
- Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Thiriart *et al.* 1989
- MF53.1: The relative affinity for denatured/native gp120 is 10. Moore *et al.* [1994c]
- No.** 365  
**MAb ID** MF58.1  
**HXB2 Location** gp160 (101–120)  
**Author Location** gp120 (101–120 LAI)  
**Epitope** VEQMHEDIISLWDQSLKPCV  
**Subtype B**  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env
- Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Thiriart *et al.* 1989
- No.** 366  
**MAb ID** MF77.1  
**HXB2 Location** gp160 (101–120)  
**Author Location** gp120 (101–120 LAI)  
**Epitope** VEQMHEDIISLWDQSLKPCV  
**Subtype B**  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env
- Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1  
**References** Moore *et al.* 1994c; Thiriart *et al.* 1989
- MF77.1: The relative affinity for denatured/native gp120 is 11. Moore *et al.* [1994c]
- No.** 367  
**MAb ID** T2.1  
**HXB2 Location** gp160 (101–120)  
**Author Location** gp120 (101–120 LAI)  
**Epitope** VEQMHEDIISLWDQSLKPCV  
**Subtype B**  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env
- Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C1

**Research Contact** Lennart Akerblom, Britta Wahren and Jorma Hinkula

**References** Moore *et al.* 1994d; Moore *et al.* 1994c; Bolmstedt *et al.* 1990; Akerblom *et al.* 1990

- T2.1: The relative affinity for denatured/native gp120 is .27 – mutations 113 D/R, 106 E/A, and 117 D/A impair binding. Moore *et al.* [1994c]

**No.** 368

**MAB ID** 11/65 (11/65a/5h)

**HXB2 Location** gp160 (102–121)

**Author Location** gp120 (311–321 HXB10)

**Epitope** EQMHEDIISLWDQSLKPCVK

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BH10

*HIV component:* gp120

**Species (Isotype)** rat (IgG2b)

**Ab Type** gp120 C1

**References** Peet *et al.* 1998; McKeating *et al.* 1993b; McKeating *et al.* 1992a

- 11/65: UK Medical Research Council AIDS reagent: ARP3076.
- 11/65: Called 11/65a/5h – The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – 11/65 was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 11/65: Binds only soluble gp120, not virion bound – used to quantify gp120 shedding – (numbering is incorrect in original?) McKeating *et al.* [1992a]

**No.** 369

**MAB ID** W1

**HXB2 Location** gp160 (102–121)

**Author Location** gp120 (102–121 LAI)

**Epitope** EQMHEDIISLWDQSLKPCVK

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Strain:* B clade LAI *HIV component:* Env

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 C1

**Research Contact** D. Weiner, U. Penn.

**References** Moore *et al.* 1994c

- W1: The relative affinity for denatured/native gp120 is 6 – mutations 113 D/A, 113 D/R, and 117 K/W impair binding. Moore *et al.* [1994c]

**No.** 370

**MAB ID** T11

**HXB2 Location** gp160 (102–125)

**Author Location** gp120 (102–125)

**Epitope** EQMHEDIISLWDQSLKPCVKLTPL

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* oligomeric gp140

**Species (Isotype)** mouse

**Ab Type** gp120 C1

**Research Contact** R. Doms, Univ. of Pennsylvania

**References** Jagodzinski *et al.* 1996; Earl *et al.* 1994

- T11: The sulfated polysaccharide, curdlan sulfate (CRDS), binds to the Envelope of T-tropic viruses and neutralizes virus – deletion of the V3 loop from gp120 results in more potent T11 inhibition by CRDS. Jagodzinski *et al.* [1996]
- T11: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 371

**MAB ID** GV1A8

**HXB2 Location** gp160 (105–113)

**Author Location** gp120 (105–113 IIIB)

**Epitope** HEDIISLWD

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein-Ab complex *HIV component:* gp120-Mab complex

**Species (Isotype)** mouse

**Ab Type** gp120 C1

**References** Denisova *et al.* 1996

- GV1A8: When anti-V3 MAb M77 was bound to gp120 and used as an immunogen, it stimulated many MAbs to linear epitopes – MAbs GV7A4 and GV5H5 are homologous to GV1A8 and were generated in the same experiment. Denisova *et al.* [1996]

**No.** 372

**MAB ID** CA13 (ARP3119)

**HXB2 Location** gp160 (106–112)

**Author Location** Env

**Epitope** EDIISLW

**Subtype** A

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* vaccinia prime with gp120 boost *Strain:* A clade *HIV component:* Env

**Species (Isotype)** mouse

**Ab Type** gp120 C1

**References** Holl *et al.* 2006a; Billington *et al.* 2007; Zipeto *et al.* 2005; Jeffs *et al.* 2004

**Keywords** dendritic cells, neutralization, subtype comparisons, vaccine antigen design

- CA13: MRC Centralized Facility for AIDS Reagents, NIBSC, UK, ARP3119.
- CA13: The MAb CA13 binds to the conserved C1 epitope EDIISLW and was used in conjunction with MAb 221, a MAb that binds to the gp120 C-terminal end, to explore the composition and stability of a highly stable trimeric rgp140 derived from a HIV-1 subtype D isolate containing intermonomer V3-derived disulfide bonds and lacking gp120/gp41 proteolytic processing. The stability of the trimer indicates it may be a good candidate for structural studies. Billington *et al.* [2007]

- CA13: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- CA13: HIV-1 fusion complexes were prepared from cell lines expressing R5 HIV-1 gp120/gp41 and CD4-CCR5. Neutralizing Abs were raised against both R5 (strain BaL) and X4 (strain 213) viruses. CA13 was used to detect gp120/gp41. Zipeto *et al.* [2005] (**vaccine antigen design**)
- CA13: A set of oligomeric envelope proteins were made from six primary isolates for potential use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. CA13 is a MAb that binds to a linear epitope in the C13 region of gp120 that was raised against clade A variant 92/UG/029. C13 bound to antigens from all clades A-F, as well as group O. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design, subtype comparisons**)

No. 373

MAb ID 11

HXB2 Location gp160 (111–120)

Author Location gp120 (101–120 LAI)

Epitope LWDQSLKPCV

Subtype B

Neutralizing

Immunogen vaccine

Strain: B clade LAI HIV component: Env

Species (Isotype) mouse (IgG)

Ab Type gp120 C1

References Moore *et al.* 1994c; Thiriart *et al.* 1989

- 11: The relative affinity for denatured/native gp120 is 7.8 – mutation 113 D/R impairs binding. Moore *et al.* [1994c]

No. 374

MAb ID 12G10

HXB2 Location gp160 (111–120)

Author Location gp120 (101–120 LAI)

Epitope LWDQSLKPCV

Subtype B

Neutralizing

Immunogen vaccine

Strain: B clade LAI HIV component: Env

Species (Isotype) mouse (IgG)

Ab Type gp120 C1

References Moore *et al.* 1994c; Thiriart *et al.* 1989

- 12G10: The relative affinity for denatured/native gp120 is 17 – mutation 117 K/W impairs binding. Moore *et al.* [1994c]

No. 375

MAb ID 135/9 (87-135/9)

HXB2 Location gp160 (111–120)

Author Location gp120 (111–120 LAI)

Epitope LWDQSLKPCV

Subtype B

Neutralizing L

Immunogen vaccine

Vector/Type: protein Strain: B clade IIIB

HIV component: gp120

Species (Isotype) mouse (IgG1)

Ab Type gp120 C1

Research Contact Matthias Niedrig

References Yang *et al.* 2000; Kropelin *et al.* 1998; Binley*et al.* 1998; Binley *et al.* 1997a; Trkola *et al.*1996a; Moore & Sodroski 1996; Moore *et al.*1994d; Moore *et al.* 1994c; Niedrig *et al.*

1992b

- 135/9: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- 135/9: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 135/9: Noted to bind to C1 peptide HEDIISLWDQSLK – blocks gp120 interaction with CD4+ cells – blocking activity is additive when combined with antibodies which bind in the C4 region of gp120 (F105, 388/389, and b12) Kropelin *et al.* [1998]
- 135/9: Binding is enhanced by some anti-C1 and anti-C5 antibodies – enhances binding of some anti-V3, anti-C4 and anti-V2 MAbs – 135/9 binds to predicted alpha-helix in C1. Moore & Sodroski [1996]
- 135/9: Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- 135/9: The relative affinity for denatured/native gp120 is 15 – mutation 113 D/R impairs binding to native and denatured, 113 D/A only to denatured. Moore *et al.* [1994c]
- 135/9: Substitutions 106 E/A, 113 D/A or R, and 117 K/W impair binding, some substitutions enhance binding. Moore *et al.* [1994d]
- 135/9: Defines the epitope as gp120(114-123) MHEDIISLWD (core LWD?) – weak neutralization of lab strain. Niedrig *et al.* [1992b]

No. 376

MAb ID 7C10

HXB2 Location gp160 (111–120)

Author Location gp120 (101–120 LAI)

Epitope LWDQSLKPCV

Subtype B

Neutralizing

Immunogen vaccine

Strain: B clade LAI HIV component: Env



**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 C1

**References** Moore *et al.* 1994c; Thiriart *et al.* 1989

- 7C10: The relative affinity for denatured/native gp120 is 5.8 – mutation 117 K/W impairs binding. Moore *et al.* [1994c]

**No.** 377

**MAb ID** C4

**HXB2 Location** gp160 (111–120)

**Author Location** gp120 (101–120 LAI)

**Epitope** LWDQSLKPCV

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI

*HIV component:* gp160

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C1

**Research Contact** George Lewis

**References** Moore *et al.* 1994c; Moore & Ho 1993; Abacioglu *et al.* 1994

- C4: C1 region – epitope boundaries mapped by peptide scanning, BH10 core IISLW. Abacioglu *et al.* [1994]
- C4: The relative affinity for denatured/native gp120 is 10. Moore *et al.* [1994c]
- C4: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

**No.** 378

**MAb ID** MF46.1

**HXB2 Location** gp160 (111–120)

**Author Location** gp120 (101–120 LAI)

**Epitope** LWDQSLKPCV

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Strain:* B clade LAI *HIV component:* Env

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 C1

**References** Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF46.1: The relative affinity for denatured/native gp120 is 8.5. Moore *et al.* [1994c]

**No.** 379

**MAb ID** 6D5

**HXB2 Location** gp160 (122–141)

**Author Location** gp120 (122–141 LAI)

**Epitope** LTPLCVSLKCTDLKNDTNTN

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Strain:* B clade LAI *HIV component:* Env

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 V2

**Research Contact** S. Nigida and L. Arthur, NCI, Frederick, MD USA

**References** Moore *et al.* 1994d; Moore *et al.* 1994c

- 6D5: The relative affinity for denatured/native gp120 is 15 – mutations Delta119-205 and 125 L/G impair binding. Moore *et al.* [1994c]

**No.** 380

**MAb ID** B33

**HXB2 Location** gp160 (123–142)

**Author Location** gp120 (123–142 LAI)

**Epitope** TPLCVSLKCTDLGNATNTNS

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade NL43

*HIV component:* gp160

**Species (Isotype)** mouse (IgG2bκ)

**Ab Type** gp120 V2

**Research Contact** Daniels

**References** Bristow *et al.* 1994; Abacioglu *et al.* 1994

- B33: UK Medical Research Council AIDS reagent: ARP304, gp160/41 binding.
- B33: There are two MAbs in the literature named B33, see also gp160(727-734) Abacioglu *et al.* [1994]
- B33: Epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]
- B27: C1 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp160 IIIB:NL43, MicroGenSys. Bristow *et al.* [1994]

**No.** 381

**MAb ID** polyclonal (VEI1)

**HXB2 Location** gp160 (131–151)

**Author Location** Env (131–151)

**Epitope** CTDLKNdTNTNSSSGRMMMEK

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Carlos *et al.* 1999

- Antibody response to the epitopes in a vaccine construct (VEI) containing peptides from 5 hypervariable regions of gp120 was detected in the sera of HIV-1 positive subjects, including sera from 6 non-subtype B infections – serum samples from San Francisco, Canada and Puerto Rico cohort showed presence of antibodies against all five VEI hypervariable regions, but most consistently against the V3 region peptide NNNTRKSIRIGPGRAFYYTTGDIGNIRQ. Carlos *et al.* [1999]

**No.** 382

**MAb ID** 35D10/D2

**HXB2 Location** gp160 (139–155)

**Author Location** gp120

**Epitope** NTKSSNWKEMDGEIK

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162

*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V1

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 35D10/D2: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yielded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 35D10/D2: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potentially neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

No. 383

**MAb ID** 40H2/C7

**HXB2 Location** gp160 (139–155)

**Author Location** gp120

**Epitope** NTKSSNWKEMDGEIK

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V1

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 40H2/C7: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yielded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 40H2/C7: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potentially neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

No. 384

**MAb ID** 43A3/E4

**HXB2 Location** gp160 (139–155)

**Author Location** gp120

**Epitope** NTKSSNWKEMDGEIK

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V1

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 43A3/E4: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yielded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 43A3/E4: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potentially neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

No. 385

**MAb ID** 43C7/B9

**HXB2 Location** gp160 (139–155)

**Author Location** gp120

**Epitope** NTKSSNWKEMDGEIK

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V1

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 43C7/B9: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yielded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs

to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)

- 43C7/B9: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potentially neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

No. 386

MAb ID 45D1/B7

HXB2 Location gp160 (139–155)

Author Location gp120

Epitope NTKSSNWKEMDGEIK

Neutralizing L

Immunogen vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V1

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 45D1/B7: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yielded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 45D1/B7: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potentially neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

No. 387

MAb ID 46E3/E6

HXB2 Location gp160 (139–155)

Author Location gp120

Epitope NTKSSNWKEMDGEIK

Neutralizing

Immunogen vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V1

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 46E3/E6: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yielded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 46E3/E6: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potentially neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

No. 388

MAb ID 58E1/B3

HXB2 Location gp160 (139–155)

Author Location gp120

Epitope NTKSSNWKEMDGEIK

Neutralizing L

Immunogen vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V1

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 58E1/B3: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yielded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 58E1/B3: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with

HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potentially neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

**No.** 389

**MAb ID** 64B9/A6

**HXB2 Location** gp160 (139–155)

**Author Location** gp120

**Epitope** NTKSSNWKEMDGEIK

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V1

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 64B9/A6: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yielded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 64B9/A6: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potentially neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

**No.** 390

**MAb ID** 69D2/A1

**HXB2 Location** gp160 (139–155)

**Author Location** gp120

**Epitope** NTKSSNWKEMDGEIK

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V1

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 69D2/A1: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yielded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 69D2/A1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potentially neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

**No.** 391

**MAb ID** 82D3/C3

**HXB2 Location** gp160 (139–155)

**Author Location** gp120

**Epitope** NTKSSNWKEMDGEIK

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V1

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 82D3/C3: In an extensive review of gp120 binding MAbs in this database, V1-specific MAbs are noted to be unusual, but in one study transgenic mouse immunization with SF162 yielded ten V1 MAbs with highly strain-specific autologous NAb responses, and V1 was immunodominant. Human MAbs to V1 may be difficult to isolate due to selection with heterologous strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 82D3/C3: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – C-term-V1- region was immunodominant in these mice and the ten V1-specific MAbs could potentially neutralize autologous strain SF162 but were highly type specific. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

**No.** 392

**MAb ID** 697-D (697D, 697-30D)  
**HXB2 Location** gp160 (161–180)  
**Author Location** gp120 (161–180 IIIB)  
**Epitope** ISTSIRGKVQKEYAFFYKLD  
**Neutralizing** P (weak)  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**Ab Type** gp120 V2  
**Research Contact** Susan Zolla-Pazner (Zolla-Pazner) (mcr6@med.nyu.edu) (NYU Med. Center) or Cellular Products Inc, Buffalo NY

**References** Holl *et al.* 2006a; Selvarajah *et al.* 2005; Gorny & Zolla-Pazner 2004; He *et al.* 2002; Maksiutov *et al.* 2002; Edwards *et al.* 2002; Nyambi *et al.* 2000; Hioe *et al.* 2000; Gorny *et al.* 2000; Stamatatos & Cheng-Mayer 1998; Nyambi *et al.* 1998; Parren *et al.* 1997b; Fouts *et al.* 1997; Binley *et al.* 1997a; Trkola *et al.* 1996a; Moore & Ho 1995; Forthal *et al.* 1995; Gorny *et al.* 1994

**Keywords** ADCC, antibody binding site definition and exposure, co-receptor, dendritic cells, enhancing activity, neutralization, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 697D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 697-D: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V2 MAb 697-D did not bind to mCHO and had diminished binding to GDMR, while V2 MAb 8.22.2 bound to GDMR but not mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- 697-D: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weak with limited cross-reactivity; it weakly neutralizes some primary but not TCLA strains. 697-D is the best characterized of the anti-V2 MAbs, and binds weakly and sporadically to isolates from clades A-D. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review, subtype comparisons**)
- 697-D: Called 697D – Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels

of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**antibody binding site definition and exposure**)

- 697-D: Called 697D – Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A, 4117C and 697D were used as controls. He *et al.* [2002]
- 697-D: This epitope is similar to a fragment of the human protein macrophage colony stimulating factor I receptor SISIR-LKVQK. Maksiutov *et al.* [2002]
- 697-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V2 MAbs 697-D, 1357 and 1361 favored the monomer by approximately 2 fold. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 697-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – V2 MAb 697-D did not effect proliferation. Hioe *et al.* [2000]
- 697-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000] (**subtype comparisons**)
- 697-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – V2 Abs 697-D, 1361, and 1357 tended to bind weakly with a similar pattern of specificity to virions, and bound well to soluble gp120: weak binding to 1/4 B clade viruses (CA5), and weak binding to viruses from subtype A and D. Nyambi *et al.* [1998] (**subtype comparisons**)
- 697-D: Called 697-30D – deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V1 or V2 did not enable neutralization by V2 MAbs G3.4, G3.136, or 687-30D. Stamatatos & Cheng-Mayer [1998] (**variant cross-recognition or cross-neutralization**)
- 697-D: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 697-D bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- 697-D: Does not neutralize TCLA strains but neutralizes some primary isolates weakly. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 697-D: Partial inhibition of gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**co-receptor**)
- 697-D: Not neutralizing, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC, enhancing activity**)

- 697-D: Review: called 697/30D – neutralizes some primary, but not lab adapted strains. Moore & Ho [1995] (**variant cross-recognition or cross-neutralization, review**)
- 697-D: Conformational with weak reactivity to V2 peptide ISTSIRGKVQKEYAFFYKLD – neutralized 3/4 primary isolates, but none of 4 lab strains – V2 substitutions 176/177 FY/AT, 179/180 LD/DL, 183/184 PI/SG, and 192-194 YSL/GSS abrogate binding – anti-C4 MAb G3-536 and G45-60 enhance binding – mild oxidation of carbohydrate moieties inhibits binding. Gorny *et al.* [1994] (**antibody binding site definition and exposure**)

No. 393

**MAb ID** 6C4/S

**HXB2 Location** gp160 (162–169)

**Author Location** gp120 (BH10)

**Epitope** STSIRGKV

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BH10

*HIV component:* gp120

**Species (Isotype)**

**Research Contact** S. Ranjbar (NIBSC, UK)

**References** Moore *et al.* 1993a

- 6C4/S: UK Medical Research Council AIDS reagent: ARP3049.

No. 394

**MAb ID** C108G (C108g)

**HXB2 Location** gp160 (162–169)

**Author Location** gp120 (162–169 HXB2)

**Epitope** STSIRGKV

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** chimpanzee (IgG1κ)

**Ab Type** gp120 V2

**Research Contact** S. Tilley, Public Health Research Institute, NY, NY

**References** Honnen *et al.* 2007; Pinter *et al.* 2005; Gorny & Zolla-Pazner 2004; Alsmadi & Tilley 1998; Mondor *et al.* 1998; Ugolini *et al.* 1997; Warrier *et al.* 1996; Warrier *et al.* 1995; Wu *et al.* 1995; Warrier *et al.* 1994

**Keywords** ADCC, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, review, variant cross-recognition or cross-neutralization

- C108G: Position 167 in V2 dictates the specificities of three type-specific neutralizing MAbs that bind to an otherwise relatively conserved epitope in involving V2: 2909, C108g, and 10/76b. Introduction of D167G mutation in YU2 Env resulted in significant neutralization by C108G. Removing of glycan at position N131 and V1 glycosylation site 140 resulted in increase in sensitivity to C108G. On the other hand, eliminating the glycan at position 160 in V2 in conjunction with V1 glycan and D167G mutations resulted in large decrease in sensitivity to C108, indicating that the glycan in this position is an important component of the C108G epitope. Honnen *et al.*

[2007] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)

- C108G: This MAb is type-specific and neutralizes BaL and HXB2. It is the most potent anti-V2 MAb, is glycan dependent, and contrary to earlier reports requires disulfide bonds. Neutralization by C108g is not mediated by CD4 or CCR5 receptor blockage on the cell surface. Binding to CD4 was inhibited by b12, but not by C108g. Binding to CCR5 was completely inhibited by two V3 MAbs, 4117C and 2219, and was substantially inhibited by 2G12, but was not inhibited by C108g. JR-FL is a neutralization resistant strain; modification of JRFL at positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potentially neutralize the modified JR-FL. The MAb 10/76b, that binds to a linear V2 epitope that is unaffected by deglycosylation or reduction eliminating disulfide bonds, could only weakly neutralize this modified JR-FL. Similarly SF162 substitutions in the neutralization sensitive virus SF162 GVK->NMK (167-169) plus the glycosylation site at 160, created a G108g neutralization sensitive virus. In contrast, 10/76b binds to the NMK substituted variant, but addition of the glycosylation site inhibited binding. Pinter *et al.* [2005] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- C108G: This MAb is unusual among V2-directed MAbs. It is glycan dependent and can neutralize both a primary isolate (BaL and a TCLA (IIIB) strain. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, review**)
- C108G: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – C108G bound and directed lysis against only IIIB – this is first demonstration of ADCC directed by a V2 specific MAb. Alsmadi & Tilley [1998] (**ADCC, variant cross-recognition or cross-neutralization**)
- C108G: Inhibits HX10 binding to both CD4 positive and negative HeLa cells. Mondor *et al.* [1998]
- C108G: Viral binding inhibition by C108G was correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997] (**antibody binding site definition and exposure**)
- C108G: Synergistic neutralization of HIV-1 when combined with anti-V3 MAbs 0.5beta and C311E, or anti-CD4BS MAbs, 1125H and 5145A – neutralization further enhanced by presence of both 1125H and 0.5beta. Warrier *et al.* [1996] (**antibody interactions**)
- C108G: Characterization of MAb variable region. Warrier *et al.* [1995] (**antibody sequence variable domain**)
- C108G: Strain specificity: LAI, BaL, HXB2 – conformational character – glycosylation site at 160 critical – mutation of conserved glycosylation site at 156 increased epitope exposure. Wu *et al.* [1995] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- C108G: Chimps were infected with HIV-1 IIIB, and this high affinity MAb was obtained from an Epstein-Barr virus transformed B-cell line. It gave potent neutralization of HIV-1 IIIB. Binding was not affected by reduction of disulfide bonds. Binding was disrupted by removal of N-linked glycans. The peptide binds with lower affinity than glycosylated Env. Warrier *et al.* [1994] (**antibody binding site definition and exposure, antibody generation**)

- No.** 395  
**MAb ID** 10/76b  
**HXB2 Location** gp160 (162–170)  
**Author Location** gp120 (162–171 BH10)  
**Epitope** STSIRGKVQ  
**Neutralizing** L (HXB10)  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)** rat (IgG2a)  
**Research Contact** Jane McKeating
- References** Honnen *et al.* 2007; Pinter *et al.* 2005; McKeating *et al.* 1996; Wu *et al.* 1995; Shotton *et al.* 1995; McKeating *et al.* 1993a; McKeating *et al.* 1993b
- Keywords** antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization
- 10/76b: UK Medical Research Council AIDS reagent: ARP3077.
  - 10/76b: Position 167 in V2 dictates the specificities of three type-specific neutralizing MAbs that bind to an otherwise relatively conserved epitope in involving V2: 2909, C108g, and 10/76b. Introduction of D167G mutation in YU2 Env resulted in weak neutralization by 10/76b. Removing the glycan at position N131 resulted in increase in sensitivity to 10/76b while removing of V1 glycosylation site 140 had minimal effect. Eliminating the glycan at position 160 in V2 in conjunction with V1 glycan and D167G mutations resulted in an increase in sensitivity to 10/76b, indicating that the glycan in this position acts as a potent masking element for the 10/76b epitope. Honnen *et al.* [2007] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 10/76b: This study is about the MAb C108g, and 10/76b was a control. C108g is type-specific and neutralizes BaL and HXB2. It is the most potent anti-V2 MAb, and is glycan dependent and contrary to earlier reports requires disulfide bonds. Neutralization by C108g is not mediated by CD4 or CCR5 receptor blockage on the cell surface. JR-FL is a neutralization resistant strain; modification of JRFL at positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potentially neutralize the modified JR-FL. The MAb 10/76b, that binds to a linear V2 epitope that is unaffected by deglycosylation or reduction eliminating disulfide bonds, could only weakly neutralize this modified JR-FL. Similarly SF162 substitutions in the neutralization sensitive virus SF162 GVK->NMK (167-169) plus the glycosylation site at 160, created a G108g neutralization sensitive virus. In contrast, 10/76b binds to the NMK substituted variant, but addition of the glycosylation site inhibited binding. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
  - 10/76b: Neutralizes HXB2, but fails to neutralize chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996]
  - 10/76b: Cross-competes with MAbs 10/76b and 11/4b – HXB2 neutralization escape mutant has the substitution I/T at residue 165. Shotton *et al.* [1995] (**antibody binding site definition and exposure**)

- 10/76b: Included in cross-competition and neutralization studies. Shotton *et al.* [1995] (**antibody binding site definition and exposure**)
- 10/76b: HX10 strain specificity – binds native, deglycosylated, or denatured gp120. Wu *et al.* [1995] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 10/76b: This MAb was obtained from a hybridoma cell line. An R to L substitution abrogated binding. Human sera recognize the 10/76 epitope. McKeating *et al.* [1993b] (**antibody generation**)

- No.** 396  
**MAb ID** 11/41e  
**HXB2 Location** gp160 (162–170)  
**Author Location** gp120 (162–171)  
**Epitope** STSIRGKVQ  
**Neutralizing** L (HXB10)  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)** rat (IgG1)  
**References** Wu *et al.* 1995; Shotton *et al.* 1995; McKeating *et al.* 1993b
- 11/41e: Included in cross-competition and neutralization studies. Shotton *et al.* [1995]
  - 11/41e: HX10 strain specificity – binds native and deglycosylated gp120. Wu *et al.* [1995]
  - 11/41e: R to L abrogated binding – human sera recognize the epitope. McKeating *et al.* [1993b]

- No.** 397  
**MAb ID** 11/4b  
**HXB2 Location** gp160 (162–170)  
**Author Location** gp120 (162–171)  
**Epitope** STSIRGKVQ  
**Neutralizing** L (HXB10)  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)** rat (IgG2a)  
**References** Moore & Sodroski 1996; Wu *et al.* 1995; Shotton *et al.* 1995; McKeating *et al.* 1993b
- 11/4b: Linear V2 epitope – reciprocal binding enhancement of anti-V2 discontinuous epitope antibodies (in contrast to BAT085) and CD4 inducible antibody 48d. Reciprocal inhibits BAT085 binding – inhibits CRA-3 binding CRA-3 does not inhibit 11/4b. Moore & Sodroski [1996]
  - 11/4b: Cross-competes with MAbs 10/76b and 11/4c – HXB2 neutralization escape mutant has the substitution I/T at residue 165. Shotton *et al.* [1995]
  - 11/4b: HXB10 strain specificity – binds native, deglycosylated, or denatured gp120. Wu *et al.* [1995]
  - 11/4b: A change from R to L abrogated binding – human sera recognize epitope. McKeating *et al.* [1993b]

- No.** 398  
**MAb ID** RSD-33  
**HXB2 Location** gp160 (162–170)  
**Author Location** gp120 (162–171)

**Epitope** STSIRGKVQ  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)**  
**Research Contact** R. Daniels (NIMR, UK)  
**References** Moore *et al.* 1993a

**No.** 399  
**MAb ID** 11/4c (11/4c/1j/4j)  
**HXB2 Location** gp160 (162–170)  
**Author Location** gp120 (152–181)  
**Epitope** STSIRGKVQ  
**Neutralizing** L (HXB2)  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)** rat (IgG2a)  
**Ab Type** gp120 V2  
**References** Peet *et al.* 1998; Shotton *et al.* 1995; Wu *et al.* 1995; McKeating *et al.* 1993b

- 11/4c: UK Medical Research Council AIDS reagent: ARP3035.
- 11/4c: Called 11/4c/1j/4j – The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – 11/4c was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 11/4c: Cross-competes with MAbs 10/76b and 11/4b – HXB2 neutralization escape mutant has the substitution I/T at residue 165. Shotton *et al.* [1995]
- 11/4c: HX10 strain specificity – binds native, deglycosylated, or denatured gp120. Wu *et al.* [1995]
- 11/4c: R to L substitution abrogated binding – human sera recognize epitope. McKeating *et al.* [1993b]

**No.** 400  
**MAb ID** 8.22.2  
**HXB2 Location** gp160 (162–178)  
**Author Location** gp120  
**Epitope** TTSIRDKVQKEYALFYK  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** transgenic mouse (IgG2κ)  
**Ab Type** gp120 V2  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org  
**References** Dhillon *et al.* 2007; Selvarajah *et al.* 2005; Pinter *et al.* 2004; Pantophlet *et al.* 2004; Gorny & Zolla-Pazner 2004; Maksiutov *et al.* 2002; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, neutralization, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 8.22.2: This Ab was used to help define the antigenic profile of envelopes used in serum depletion experiments to attempt to define the neutralizing specificities of broadly cross-reactive neutralizing serum. This Ab bound to JR-FL and JR-CSF gp120 monomers but not to core JR-CSF gp120 monomer used in the same experiments. V1, V2, and V3 specificities did not contribute to the broadly neutralizing capability of sera from 3 (2 B clade, 1 A clade) HIV infected individuals. Dhillon *et al.* [2007] (**antibody binding site definition and exposure, neutralization**)
- 8.22.2: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V2 MAb 697-D did not bind to mCHO and had diminished binding to GDMR, while V2 MAb 8.22.2 bound to GDMR but not mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- 8.22.2: This broad review of anti-Envelope MAbs notes that V2 MAbs are generally weakly neutralizing at best, and somewhat strain specific. 8.22.2 weakly neutralizes SF162. Gorny & Zolla-Pazner [2004] (**review**)
- 8.22.2: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 8.22.2. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 8.22.2: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-V2 MAb were tested – 8.22.2 weakly neutralized SF162, and did not neutralize JRFL at all. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 8.22.2 : Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with



- HIV SF162 gp120 – several of the MAbs obtained were effective at neutralizing the autologous strain – 8.22.2 was the only V2-specific MAb created and it could cross-compete with MAb 697D – 8.22.2 could cross-react with BaL and JR-FL, two B clade R5 strains, but not B clade X4 or E clade viruses, and it could weakly neutralize autologous strain SF162. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 8.22.2: This epitope is similar to a fragment of the human protein macrophage colony stimulating factor I receptor SISIR-LKVQK. Maksutov *et al.* [2002]

**No.** 401  
**MAb ID** 12b  
**HXB2 Location** gp160 (162–181)  
**Author Location** gp120 (162–181)  
**Epitope** STSIRGKVQKEYAFFYKLDI  
**Neutralizing** L (HXB10)  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)** rat (IgG2a)  
**Ab Type** gp120 V2  
**References** Maksutov *et al.* 2002; McKeating *et al.* 1996; Shotton *et al.* 1995

- 12b: This epitope is similar to a fragment of the human protein macrophage colony stimulating factor I receptor SISIR-LKVQK. Maksutov *et al.* [2002]
- 12b: Neutralizes HXB2, but fails to neutralize chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996]
- 12b: V2 MAb neutralized HXB2 – position 179-180 LD to DL abrogates binding – competes with 60b, but not 74. Shotton *et al.* [1995]

**No.** 402  
**MAb ID** G3-136 (G3.136)  
**HXB2 Location** gp160 (170–180)  
**Author Location** gp120 (170–180 IIIB)  
**Epitope** QKEYAFFYKLD  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 V2  
**Research Contact** Tanox Biosystems Inc and David Ho, ADARC, NY  
**References** Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Ly & Stamatatos 2000; Stamatatos & Cheng-Mayer 1998; Parren *et al.* 1998a; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Stamatatos *et al.* 1997; Binley *et al.* 1997a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Stamatatos & Cheng-Mayer 1995; Sattentau & Moore 1995; Yoshiyama *et al.* 1994; Moore *et al.* 1993a; Moore & Ho 1993; Thali *et al.* 1993; Pirofski *et al.* 1993; Fung *et al.* 1992  
**Keywords** antibody interactions, vaccine antigen design

- G3-136: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- G3-136: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V2 MAb used. Zwick *et al.* [2003] (**antibody interactions**)
- G3-136: Called G3.136 – SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000]
- G3-136: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-136: Called G3.136 – deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V1 or V2 did not enable neutralization by V2 MAbs G3.4, G3.136, or 687-30D. Stamatatos & Cheng-Mayer [1998]
- G3-136: Called G3.136 – does not mediate gp120 virion dissociation in contrast to anti-V2 MAb G3-4 – not neutralizing for SF162 or SF128A in either primary macrophages or PBMC. Stamatatos *et al.* [1997]
- G3-136: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997]
- G3-136: Described epitope as STSIRGKVQKEYAFFYKLDI – binds oligomer – binding of V2 MAbs G3-136, G3-4 or BAT123 did not significantly alter gp120 dissociation from virus or expose the gp41 epitope of MAb 50-69, in contrast to anti-V3 MAbs. Poignard *et al.* [1996a]
- G3-136: Bound preferentially to the monomeric rather than oligomeric form of LAI gp120 – neutralizes cell free Hx10. Sattentau & Moore [1995]

- G3-136: The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – V2 loop epitopes are somewhat occluded in the oligomeric gp120 epitopes on the virion surface relative to the gp120 monomer as indicated by an increase in the half-maximal binding values to macrophage-tropic isolates SF162 and SF128a – anti-V2 MAbs G3-4 and G3.136 don't bind to T-cell tropic SF2. Stamatatos & Cheng-Mayer [1995]
- G3-136: HIV-1 RF V2 substitutions 177 Y/H and 179 L/P in the V2 loop of RF reduce affinity. Yoshiyama *et al.* [1994]
- G3-136: Conformational, does not bind well to denatured gp120 – not reactive with SF-2 gp120, and does not inhibit HIV-1 sera from binding to IIIB gp120. Moore & Ho [1993]
- G3-136: Marginal binding to peptide, binding inhibited by 183/184 PI/SG substitution. Moore *et al.* [1993a]
- G3-136: Binding enhanced by selected antibodies to C1, C4, C5, V3 and anti-CD4 binding site MAbs – enhances binding of selected V3, C4 and anti-CD4 binding site MAbs. Moore *et al.* [1993a]
- G3-136: V2 region – binds and neutralizes IIIB and RF in CEM-SS cells, but not MN – neutralization activity against a few primary isolates in PBMC – sCD4 binding inhibits binding (contrast with BAT085) – deglycosylation or reduction of gp120 by DTT diminishes reactivity. Fung *et al.* [1992]

No. 403

Mab ID G3-4 (G3.4)

HXB2 Location gp160 (170–180)

Author Location gp120 (170–180 BH10)

Epitope QKEYAFFYKLD

Neutralizing L

Immunogen vaccine

Vector/Type: protein Strain: B clade IIIB  
HIV component: gp120

Species (Isotype) mouse (IgG2bk)

Ab Type gp120 V2

Research Contact Tanox Biosystems Inc and David Ho,  
ADARC, NY

References Gorny *et al.* 2005; Pantophlet *et al.* 2004; McCaffrey *et al.* 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Srivastava *et al.* 2002; Ly & Stamatatos 2000; Stamatatos & Cheng-Mayer 1998; Parren *et al.* 1998a; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Stamatatos *et al.* 1997; Binley *et al.* 1997a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Jagodzinski *et al.* 1996; Sattentau & Moore 1995; Wu *et al.* 1995; Stamatatos & Cheng-Mayer 1995; Yoshiyama *et al.* 1994; Thali *et al.* 1994; Gorny *et al.* 1994; Moore *et al.* 1994b; Moore *et al.* 1993a; Thali *et al.* 1993; Sattentau *et al.* 1993; Sullivan *et al.* 1993; Moore & Ho 1993; McKeating *et al.* 1992a; Fung *et al.* 1992; Ho *et al.* 1992; Ho *et al.* 1991a

Keywords antibody binding site definition and exposure, antibody interactions, vaccine antigen design

- G3-4: 2909 is a human anti-Env NAb that was selected by neutralization assay and binds to the quaternary structure on the intact virion. G3-4 was used as a positive control for defining the binding properties of 2909. Gorny *et al.* [2005]
- G3-4: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The SF2 and all five glycan mutants were resistant to G3-4. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure, vaccine antigen design**)
- G3-4: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including G3-4. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- G3-4: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- G3-4: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V2 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- G3-4: Called G3.4 – Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – G3.4 recognized o-gp140. Srivastava *et al.* [2002]
- G3-4: Called G3.4 – SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutral-

- ization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000]
- G3-4: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
  - G3-4: Called G3.4 – Deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V1 or V2 did not enable neutralization by V2 MAbs G3.4, G3.136, or 687-30D. Stamatatos & Cheng-Mayer [1998]
  - G3-4: Called G3.4 – mediates gp120 virion dissociation in contrast to anti-V2 MAb G3-136 – not neutralizing for SF162 or SF128A in either primary macrophages or PBMC. Stamatatos *et al.* [1997]
  - G3-4: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997]
  - G3-4: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – deletion of the V3 loop from gp120 results in more potent G3-4 binding inhibition by CRDS – G3-4 epitope described as 176-184 FYKLDIPI and 191-193 YSL. Jagodzinski *et al.* [1996]
  - G3-4: Binding enhanced by selected antibodies to C1, C4, C5, V3 and anti-CD4 binding site MAbs – enhances binding of selected V3, C4 and anti-CD4 binding site MAbs. Moore & Sodroski [1996]
  - G3-4: Described epitope as STSIRGKVKEYAFFYKLDI – binds oligomer – binding of V2 MAbs G3-136, G3-4 or BAT085 did not significantly alter gp120 dissociation from virus or expose the gp41 epitope of MAb 50-69, in contrast to anti-V3 MAbs. Pognard *et al.* [1996a]
  - G3-4: Bound preferentially to the monomeric rather than oligomeric form of LAI gp120 – neutralizes Hx10 cell-free virus. Sattentau & Moore [1995]
  - G3-4: The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – V2 loop epitopes are somewhat occluded in the oligomeric gp120 epitopes on the virion surface relative to the gp120 monomer as indicated by an increase in the half-maximal binding values to macrophage-tropic isolates SF162 and SF128a – anti-V2 MAbs G3-4 and G3.136 don't bind to T-cell tropic SF2. Stamatatos & Cheng-Mayer [1995]
  - G3-4: Reactive with BH10, RF, and MN – binds native, but not denatured or deglycosylated gp120, binds to deglycosylated V1V2 fusion protein, suggesting importance of glycans outside the V1V2 region. Wu *et al.* [1995]
  - G3-4: Weakly neutralizing, IC 50 = 53 mug/ml. Gorny *et al.* [1994]
  - G3-4: Conformationally sensitive – sporadic cross-reactivity among, and outside, B clade gp120s. Moore *et al.* [1994b]
  - G3-4: gp41 mutation (582 A/T) that reduces neutralization of anti-CD4 binding site MAbs does not alter G3-4s ability to neutralize. Thali *et al.* [1994]
  - G3-4: Neutralizes RF – substitutions 177 Y/H and 179 L/P in the V2 loop of RF reduce affinity and result in neutralization escape. Yoshiyama *et al.* [1994]
  - G3-4: Conformational, does not bind well to denatured gp120 – not reactive with SF-2 gp120, and does not inhibit HIV-1 sera from binding to IIIB gp120. Moore & Ho [1993]
  - G3-4: V2 region, marginal binding to peptide, binding inhibited by 183/184 PI/SG substitution. Moore *et al.* [1993a]
  - G3-4: Increased binding in the presence of sCD4. Sattentau *et al.* [1993]
  - G3-4: Substitutions in residues 176 to 184 affect MAb recognition – substitutions in V2 can result in gp120-gp41 dissociation. Sullivan *et al.* [1993]
  - G3-4: Neutralizes IIIB and RF, not MN – blocks sCD4-gp120, not as potent as MAb 15e – V2 binding MAbs BAT085 and G3-136 block G3-4 gp120 binding – sensitive to reduction of gp120 by DTT. Ho *et al.* [1992]
  - G3-4: Binding is sensitive to removal of glycans by endo H – 50% neutralization of 4/9 primary isolates – has conformational features. Ho *et al.* [1991a]
- No. 404**  
**MAb ID** BAT085 (BAT-085)  
**HXB2 Location** gp160 (171–180)  
**Author Location** gp120 (170–180 IIIB)  
**Epitope** KEYAFFYKLD  
**Neutralizing L**  
**Immunogen** vaccine  
*Vector/Type:* inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1  
**Species (Isotype)** mouse (IgG1)  
**Research Contact** Tanox Biosystems Inc and David Ho, ADARC, NY
- References** Parren *et al.* 1998a; Ditzel *et al.* 1997; Binley *et al.* 1997a; Pognard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Wu *et al.* 1995; Yoshiyama *et al.* 1994; Gorny *et al.* 1994; Moore *et al.* 1994d; D'Souza *et al.* 1994; Moore *et al.* 1993a; Thali *et al.* 1993; Pirofski *et al.* 1993; Moore & Ho 1993; Fung *et al.* 1992; Fung *et al.* 1987
- BAT085: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
  - BAT085: Binding is blocked by other V2 region antibodies, enhanced by several anti-C1 MAbs, and anti-V3 MAb G511 – reciprocal enhancement of CD4i MAb 48d binding. Moore & Sodroski [1996]
  - BAT085: Epitope suggested to be QKEYAFFYKLD – binds oligomer – binding of V2 MAbs G3-136, G3-4 or BAT123 did not significantly alter gp120 dissociation from virus or expose the gp41 epitope of MAb 50-69, in contrast to anti-V3 MAbs. Pognard *et al.* [1996a]

- BAT085: Bound preferentially to the monomeric rather than oligomeric form of LAI gp120 – neutralizes cell free Hx10. Sattentau & Moore [1995]
- BAT085: HXB10 strain specificity – binds native, deglycosylated, or denatured gp120. Wu *et al.* [1995]
- BAT085: Multi-lab study for antibody characterization and assay comparison – did not bind MN or SF2. D'Souza *et al.* [1994]
- BAT085: Interacts with two overlapping peptides with region of overlap KEYAFFYKLD. Gorny *et al.* [1994]
- BAT085: Neutralizes RF – substitution 177 Y/H in the V2 loop of RF does not inhibit neutralization, in contrast to MAbs G3-4 and SC258. Yoshizawa *et al.* [1994]
- BAT085: Called BAT-85 – conformational, does not bind well to denatured gp120 – not reactive with SF-2 gp120, and does not inhibit HIV-1 sera from binding to IIIB gp120. Moore & Ho [1993]
- BAT085: 7/8 V2 murine MAbs required gp120 native structure to bind, but BAT085 was the exception – type-specific. Moore *et al.* [1993a]
- BAT085: Peptide affinities of G3-136 and G3-4 are 100-fold less than BAT085, but BAT085 has lower affinity for BH10 gp120 and is weaker at neutralization. Moore *et al.* [1993a]
- BAT085: V2 region – sCD4 does not block – neutralizes IIIB and some primary isolates, but not MN or RF – binds MN – deglycosylation or DDT reduction of gp120 does not diminish reactivity. Fung *et al.* [1992]

No. 405

MAb ID 60b

HXB2 Location gp160 (172–181)

Author Location gp120 (172–181 HXB2)

Epitope EYAFFYKLDI

Subtype B

Neutralizing no

Immunogen vaccine

Vector/Type: protein Strain: B clade BH10

HIV component: gp120

Species (Isotype) rat (IgG2b)

References Shotton *et al.* 1995

- 60b: V2 MAb did not neutralize HXB2 – bound to rgp120 in ELISA – substitutions 179-180 LD/DL and 191-193 YSL/GSS abrogate binding, as do changes outside the minimum epitope – competes with 12b, but not 74. Shotton *et al.* [1995]

No. 406

MAb ID 74

HXB2 Location gp160 (172–181)

Author Location gp120 (172–181)

Epitope EYAFFYKLDI

Neutralizing no

Immunogen vaccine

Vector/Type: protein Strain: B clade BH10

HIV component: gp120

Species (Isotype) rat (IgG1)

References Shotton *et al.* 1995

- 74: V2 MAb did not neutralize HXB2 – did not bind rgp120 ELISA – position 179-180 LD to DL abrogates binding, as do changes outside the minimum epitope – does not compete with 60b or 12b, and is enhanced by two conformation dependent MAbs. Shotton *et al.* [1995]

No. 407

MAb ID 38/12b

HXB2 Location gp160 (172–191)

Author Location gp120 (172–191 HXB2)

Epitope EYAFFYKLDIIPIDNDTTSY

Subtype B

Neutralizing

Immunogen vaccine

Vector/Type: protein Strain: B clade BH10

HIV component: gp120

Species (Isotype) rat

References Wu *et al.* 1995

- 38/12b: Broad specificity: HXB2, MN, SF162 – binds native and deglycosylated gp120. Wu *et al.* [1995]

No. 408

MAb ID 38/60b

HXB2 Location gp160 (172–191)

Author Location gp120 (172–191 HXB2)

Epitope EYAFFYKLDIIPIDNDTTSY

Subtype B

Neutralizing

Immunogen vaccine

Vector/Type: protein Strain: B clade BH10

HIV component: gp120

Species (Isotype) rat

References Wu *et al.* 1995

- 38/60b: Strain specificity: HXB2 – binds native and deglycosylated gp120. Wu *et al.* [1995]

No. 409

MAb ID polyclonal (VEI2)

HXB2 Location gp160 (176–196)

Author Location Env

Epitope FYKLDIVPIDNTTTSYRLISC

Neutralizing

Immunogen HIV-1 infection

Species (Isotype) human

References Carlos *et al.* 1999

- Antibody response to the epitopes in a vaccine construct (VEI) containing peptides from 5 hypervariable regions of gp120 was detected in the sera of HIV-1 positive subjects, including sera from 6 non-subtype B infections – serum samples from San Francisco, Canada and Puerto Rico cohort showed presence of antibodies against all five VEI hypervariable regions, but most consistently against the V3 region peptide NNNTRKSIRIGPGRAFYTGGDIGNIRQ. Carlos *et al.* [1999]

No. 410

MAb ID 322-151

HXB2 Location gp160 (211–221)

Author Location gp120 (201–220 LAI)

Epitope EPIPIHYCAPA

**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Research Contact** G. Robey, Abbot Labs  
**References** Moore *et al.* 1994d; Moore *et al.* 1994c  
 • 322-151: The relative affinity denatured/native gp120 is 30. Moore *et al.* [1994c]

**No.** 411  
**MAb ID** 3D3.B8  
**HXB2 Location** gp160 (211–221)  
**Author Location** gp120 (211–220 LAI)  
**Epitope** EPIPIHYCAPA  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**References** Moore *et al.* 1994c; Bolmstedt *et al.* 1990  
 • 3D3.B8: The relative affinity denatured/native gp120 is greater than 10. Moore *et al.* [1994c]

**No.** 412  
**MAb ID** 4C11.D8  
**HXB2 Location** gp160 (211–221)  
**Author Location** gp120 (211–220 LAI)  
**Epitope** EPIPIHYCAPA  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** mouse (IgM)  
**References** Moore *et al.* 1994c; Bolmstedt *et al.* 1990  
 • 4C11.D8: The relative affinity denatured/native gp120 is greater than 10. Moore *et al.* [1994c]

**No.** 413  
**MAb ID** 493-156  
**HXB2 Location** gp160 (211–230)  
**Author Location** gp120 (211–230 LAI)  
**Epitope** EPIPIHYCAPAGFAILKCNN  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Research Contact** G. Robey, Abbot Labs  
**References** Moore *et al.* 1994c  
 • 493-156: The relative affinity denatured/native gp120 is >10. Moore *et al.* [1994c]

**No.** 414  
**MAb ID** 110.1  
**HXB2 Location** gp160 (212–221)  
**Author Location** gp120 (200–217)  
**Epitope** PIPIHYCAPA  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** human  
**References** Valenzuela *et al.* 1998; Pincus *et al.* 1996; Pincus & McClure 1993  
 • 110.1 database comment: There is another antibody with this ID that binds to Env at positions 491-500 in LAI.  
 • 110.1: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding – 110.1-RAC did not mediate cell killing, and sCD4 has no effect. Pincus & McClure [1993]; Pincus *et al.* [1996]

**No.** 415  
**MAb ID** GV4H3  
**HXB2 Location** gp160 (219–226)  
**Author Location** gp120 (219–226 IIIB)  
**Epitope** APAGFAIL  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein-Ab complex *HIV component:* gp120-Mab complex  
**Species (Isotype)** mouse  
**References** Denisova *et al.* 1996  
 • GV4H3: When anti-V3 MAb M77 was bound to gp120 and used as an immunogen, it stimulated many MAbs to linear epitopes. Denisova *et al.* [1996]

**No.** 416  
**MAb ID** J1  
**HXB2 Location** gp160 (222–231)  
**Author Location** gp120 (222–231 LAI)  
**Epitope** GFAILKCNNK  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade LAI  
**Species (Isotype)** mouse (IgG1)  
**Research Contact** J. Hoxie, U. Penn.  
**References** Cook *et al.* 1994; Moore *et al.* 1994d; Moore *et al.* 1994c  
 • J1: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]  
 • J1: The relative affinity denatured/native gp120 is 30. Moore *et al.* [1994c]

**No.** 417  
**MAb ID** J3  
**HXB2 Location** gp160 (222–231)  
**Author Location** gp120 (222–231 LAI)  
**Epitope** GFAILKCNNK  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade LAI  
**Species (Isotype)** mouse (IgG1)  
**Research Contact** J. Hoxie, U. Penn.  
**References** Cook *et al.* 1994; Moore *et al.* 1994c

- J3: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]
- J3: The relative affinity denatured/native gp120 is 30. Moore *et al.* [1994c]

No. 418

MAB ID 1006-30-D

HXB2 Location gp160 (236–245)

Author Location gp120 (241–251)

Epitope KGSKKNVSTV

Neutralizing

Immunogen

Species (Isotype) human (IgG1 $\lambda$ )

Ab Type gp120 C2

References Nyambi *et al.* 2000; Hioe *et al.* 2000

- 1006-30-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – C2 MAbs 1006-30-D and 847-D did not effect proliferation. Hioe *et al.* [2000]
- 847-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including two C2 MAbs – the binding of anti-C2 MAbs was weak to isolates from clades B, C, D, E, F, G, and they did not bind to isolates from subtypes A and H – epitope is suggested to be in a 20 amino acid peptide KGSKKNVSTVQCTHGIRPVV. Nyambi *et al.* [2000]

No. 419

MAB ID 847-D (847-30)

HXB2 Location gp160 (236–245)

Author Location gp120 (241–251)

Epitope KGSKKNVSTV

Neutralizing

Immunogen

Species (Isotype) human (IgG1 $\lambda$ )

Ab Type gp120 C2

References Holl *et al.* 2006a; Nyambi *et al.* 2000; Hioe *et al.* 2000

Keywords dendritic cells, neutralization

- 847-30: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 847-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – C2 MAbs 1006-30-D and 847-D did not effect proliferation. Hioe *et al.* [2000]
- 847-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including two C2 MAbs – the binding of anti-C2 MAbs was weak to isolates from clades B, C, D, E, F, G, and they did not bind to isolates from subtypes A and H – epitope is suggested to be in a 20 amino acid peptide KGSKKNVSTVQCTHGIRPVV. Nyambi *et al.* [2000]

No. 420

MAB ID MF169.1

HXB2 Location gp160 (252–261)

Author Location gp120 (242–261 LAI)

Epitope RPVVSTQLLL

Subtype B

Neutralizing

Immunogen vaccine

Strain: B clade LAI HIV component: Env

Species (Isotype) mouse (IgG)

References Moore *et al.* 1994d; Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF169.1: The relative affinity denatured/native gp120 is 11 – mutations 252 R/W, 257 T/G, and 257 T/R impair binding. Moore *et al.* [1994c]

No. 421

MAB ID MF170.1

HXB2 Location gp160 (252–261)

Author Location gp120 (242–261 LAI)

Epitope RPVVSTQLLL

Subtype B

Neutralizing

Immunogen vaccine

Strain: B clade LAI HIV component: Env

Species (Isotype) mouse (IgG)

References Moore *et al.* 1994d; Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF170.1: The relative affinity denatured/native gp120 is 15 – mutations 252 R/W, 257 T/G, and 257 T/R impair binding to denatured and native gp120, and 262N/T, 269 E/L and 281 A/V to only native gp120. Moore *et al.* [1994c]

No. 422

MAB ID MF87.1

HXB2 Location gp160 (252–261)

Author Location gp120 (242–261 LAI)

Epitope RPVVSTQLLL

Subtype B

Neutralizing

Immunogen vaccine

Strain: B clade LAI HIV component: Env

Species (Isotype) mouse (IgG)

References Moore *et al.* 1994c; Thiriart *et al.* 1989

- MF87.1: The relative affinity denatured/native gp120 is 10 – mutations 252 R/W, 257 T/G, and 257 T/R impair binding. Moore *et al.* [1994c]

No. 423

MAB ID 213.1

HXB2 Location gp160 (252–261)

Author Location gp120 (242–261 LAI)

Epitope RPVVSTQLLL

Subtype B

Neutralizing

Immunogen vaccine

Vector/Type: protein HIV component: Env

Species (Isotype) mouse (IgG1)

Ab Type gp120 C2

Research Contact Claudine Bruck

**References** Moore *et al.* 1994c; Moore & Ho 1993; Thiriart *et al.* 1989

- 213.1: UK Medical Research Council AIDS reagent: ARP334.
- 213.1: The relative affinity denatured/native gp120 is 100 – mutations 252 R/W, 257 T/G or T/R impair binding. Moore *et al.* [1994c]
- 213.1: Bound preferentially to denatured IIIB and SF2 gp120. Moore & Ho [1993]

**No.** 424

**MAb ID** B12

**HXB2 Location** gp160 (252–271)

**Author Location** gp120 (252–271 LAI)

**Epitope** RPVVSTQLLLLNGSLAEEEEVV

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 C2

**References** Maksutov *et al.* 2002; Moore *et al.* 1994c

- B12: This epitope is similar to a fragment of human protein lymphatic endothelium-specific hyaluronan receptor LYVE-1, TTRLLVQGSRAEE. Maksutov *et al.* [2002]
- B12: C2 region – the relative affinity for denatured/native gp120 is 27 – mutations 257 T/R and 262 N/T impair binding. Moore *et al.* [1994c]

**No.** 425

**MAb ID** B13 (Bh13, Chessie B13)

**HXB2 Location** gp160 (252–271)

**Author Location** gp120 (252–271 LAI)

**Epitope** RPVVSTQLLLLNGSLAEEEEVV

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG2a)

**Ab Type** gp120 C2

**Research Contact** George Lewis, Institute of Human Virology, Baltimore MD, USA

**References** Maksutov *et al.* 2002; Wang *et al.* 2002c; Connor *et al.* 1998; Pincus *et al.* 1996; Moore *et al.* 1994d; Abacioglu *et al.* 1994; Moore *et al.* 1994c; Moore & Ho 1993; Pincus & McClure 1993

- B13: This epitope is similar to a fragment of human protein lymphatic endothelium-specific hyaluronan receptor LYVE-1, TTRLLVQGSRAEE. Maksutov *et al.* [2002]
- B13: Called Bh13 – binds to gp120 but not to infected cells – when linked to ricin A, the immunotoxin did not mediate cell killing – sCD4 has no effect. Pincus & McClure [1993]; Pincus *et al.* [1996]
- B13: C2 region – epitope boundaries mapped by peptide scanning. core epitope: TQLLLN. Abacioglu *et al.* [1994]

- B13: The relative affinity for denatured/native gp120 is 30 – mutations 257 T/R and 269 E/L impair binding. Moore *et al.* [1994c]

- B13: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

**No.** 426

**MAb ID** C13

**HXB2 Location** gp160 (252–271)

**Author Location** gp120 (252–271 LAI)

**Epitope** RPVVSTQLLLLNGSLAEEEEVV

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C2

**Research Contact** George Lewis

**References** Maksutov *et al.* 2002; Abacioglu *et al.* 1994; Moore *et al.* 1994c; Moore & Ho 1993

- C13: NIH AIDS Research and Reference Reagent Program: 1209.

- C13: This epitope is similar to a fragment of human protein lymphatic endothelium-specific hyaluronan receptor LYVE-1, TTRLLVQGSRAEE. Maksutov *et al.* [2002]

- C13: Epitope boundary extended to RPVVSTQLLLLNGSLAEEEEVVIR, to take into account the effect of a point mutation. Abacioglu *et al.* [1994]

- C13: The relative affinity for denatured/native gp120 is 36 – mutations 257 T/R, 267 E/L, and 269 E/L impair binding. Moore *et al.* [1994c]

- C13: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

**No.** 427

**MAb ID** M89

**HXB2 Location** gp160 (252–271)

**Author Location** gp120 (252–271 LAI)

**Epitope** RPVVSTQLLLLNGSLAEEEEVV

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Env

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C2

**Research Contact** Fulvia di Marzo Veronese

**References** Maksutov *et al.* 2002; Moore *et al.* 1994d; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992

- M89: This epitope is similar to a fragment of human protein lymphatic endothelium-specific hyaluronan receptor LYVE-1, TTRLLVQGSRAEE. Maksutov *et al.* [2002]

- M89: C2 region – the relative affinity for denatured/native gp120 is >30 – mutations 257 T/R and 269 E/L impair binding. Moore *et al.* [1994c]

- M89: Immunoblot reactive, RIP negative, for strains IIIB, 451, MN, RF, and RUTZ. di Marzo Veronese *et al.* [1992]

**No.** 428

**MAb ID** B21  
**HXB2 Location** gp160 (257–262)  
**Author Location** gp120 (257–262 BH10)  
**Epitope** TQLLLN  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C2  
**References** Abacioglu *et al.* 1994  
 • B21: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

**No.** 429  
**MAb ID** B23  
**HXB2 Location** gp160 (257–262)  
**Author Location** gp120 (257–262 BH10)  
**Epitope** TQLLLN  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG2a)  
**Ab Type** gp120 C2  
**References** Abacioglu *et al.* 1994  
 • B23: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

**No.** 430  
**MAb ID** B24  
**HXB2 Location** gp160 (257–262)  
**Author Location** gp120 (257–262 BH10)  
**Epitope** TQLLLN  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG2a)  
**Ab Type** gp120 C2  
**References** Abacioglu *et al.* 1994  
 • B24: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

**No.** 431  
**MAb ID** B25  
**HXB2 Location** gp160 (257–262)  
**Author Location** gp120 (257–262 BH10)  
**Epitope** TQLLLN  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C2  
**References** Abacioglu *et al.* 1994  
 • B25: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

**No.** 432

**MAb ID** B3  
**HXB2 Location** gp160 (257–262)  
**Author Location** gp120 (257–262 BH10)  
**Epitope** TQLLLN  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C2  
**References** Abacioglu *et al.* 1994  
 • B3: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

**No.** 433  
**MAb ID** B26  
**HXB2 Location** gp160 (257–263)  
**Author Location** gp120 (257–263 BH10)  
**Epitope** TQLLLNG  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C2  
**References** Abacioglu *et al.* 1994  
 • B26: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

**No.** 434  
**MAb ID** B29  
**HXB2 Location** gp160 (257–263)  
**Author Location** gp120 (257–263 BH10)  
**Epitope** TQLLLNG  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG2a)  
**Ab Type** gp120 C2  
**References** Abacioglu *et al.* 1994  
 • B29: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

**No.** 435  
**MAb ID** B36  
**HXB2 Location** gp160 (257–263)  
**Author Location** gp120 (257–263 BH10)  
**Epitope** TQLLLNG  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 C2  
**References** Abacioglu *et al.* 1994  
 • B36: C2 region, epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

**No.** 436



**MAb ID** 110.E  
**HXB2 Location** gp160 (262–281)  
**Author Location** gp120 (262–281 LAI)  
**Epitope** NGLSLAEVVIRSVNFTDNA  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C2  
**Research Contact** F. Traincard  
**References** Maksutov *et al.* 2002; Moore *et al.* 1994d; Moore *et al.* 1994c

- 110.E: This epitope is similar to a fragment of human protein lymphatic endothelium-specific hyaluronan receptor LYVE-1, TTRLLVQGSLRAEE. Maksutov *et al.* [2002]
- 110.E: The relative affinity for denatured/native gp120 is 7.3. Moore *et al.* [1994c]

**No.** 437  
**MAb ID** 110.C  
**HXB2 Location** gp160 (271–280)  
**Author Location** gp120 (271–280 LAI)  
**Epitope** VIRSVNFTDN  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C2  
**Research Contact** F. Traincard, Hybridolabs, Institut Pasteur  
**References** Valenzuela *et al.* 1998; Moore *et al.* 1994d; Moore *et al.* 1994c

- 110.C: Only slightly reduces LAI viral binding or entry into CEM cells. Valenzuela *et al.* [1998]
- 110.C: The relative affinity for denatured/native gp120 is 1. Moore *et al.* [1994c]

**No.** 438  
**MAb ID** IIIB-V3-26  
**HXB2 Location** gp160 (291–307)  
**Author Location** gp120 (299–304 IIIB)  
**Epitope** SVEINCTRPNNTRKSI  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade IIIB  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 V3  
**References** Maksutov *et al.* 2002; Laman *et al.* 1992

- IIIB-V3-26: This epitope is similar to a fragment of the FasI receptor precursor (Apptosis-mediating surface antigen fas) (APO- 1 antigen) (CD95 antigen), VEINCTRQN. Maksutov *et al.* [2002]
- IIIB-V3-26: Binds to the base of the V3 loop on denatured gp120. Laman *et al.* [1992]

**No.** 439  
**MAb ID** IIIB-V3-21 (V3-21)

**HXB2 Location** gp160 (294–299)  
**Author Location** gp120 (299–304 IIIB)  
**Epitope** INCTRP  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade IIIB  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 V3  
**Research Contact** J. Laman  
**References** Ling *et al.* 2004; Maksutov *et al.* 2002; Zhang *et al.* 2002; Valenzuela *et al.* 1998; Laman *et al.* 1993; Laman *et al.* 1992

**Keywords** antibody binding site definition and exposure

- IIIB-V3-21: UK Medical Research Council AIDS reagent: ARP3048.
- IIIB-V3-21: NIH AIDS Research and Reference Reagent Program: 1725.
- IIIB-V3-21: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of the V3 MAbs 694-98D and 447-52D, that both bind near the tip of the loop, was decreased by both thrombin and trypsin, but anti-V3 MAb IIIB-V3-21 was not decreased in either case. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- IIIB-V3-21: This epitope is similar to a fragment of the FasI receptor precursor (Apptosis-mediating surface antigen fas) (APO- 1 antigen) (CD95 antigen), VEINCTRQN. Maksutov *et al.* [2002]
- IIIB-V3-21: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- IIIB-V3-21: Does not block HIV-1 LAI binding or entry into CEM cells. Valenzuela *et al.* [1998]
- IIIB-V3-21: Binds to NP40 treated gp120, and epitope is probably obscured by local glycosylation. Laman *et al.* [1993]
- IIIB-V3-21: Binds to the base of the V3 loop on denatured gp120. Laman *et al.* [1992]

**No.** 440  
**MAb ID** 168B8  
**HXB2 Location** gp160 (296–317)  
**Author Location** gp120 (BaL)  
**Epitope** CTRPNYNKRKHIGPGRAF  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* gp120-CD4 complex *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** humanized mouse (IgG2κ)

**Ab Type** gp120 V3

**Research Contact** Abraham Pinter, Lab. of Retrovirology, Public Research Institute, pinter@phri.org

**References** He *et al.* 2003

**Keywords** antibody binding site definition and exposure, vaccine antigen design

- 168B8: Vaccination of a gp120-CD4 fusion complex in six transgenic XMG2 XenoMouse mice that produce human IgG2 with K light chain did not produce any neutralizing antibodies. 36/39 MAbs derived from one of these mice were in one of two competition groups that were conformational and specific for the complex, suggesting this chimeric vaccine may be of little value, as immunodominant responses are to epitopes unique to the complex, not present in native Env. This MAb is one of the 3/36 non-neutralizing MAbs that bound to linear epitopes on gp120. He *et al.* [2003] (**antibody binding site definition and exposure, vaccine antigen design**)

**No.** 441

**MAb ID** polyclonal

**HXB2 Location** gp160 (296–331)

**Author Location** gp120 (MN)

**Epitope** CNYNKRKRIHIGPGRAFYTCKNIIGTIC

**Neutralizing** L

**Immunogen**

**Species (Isotype)** rabbit (IgA, IgG)

**Ab Type** gp120 V3

**References** FitzGerald *et al.* 1998

- Polyclonal response to MN, or Thai E V3 loop inserted into Pseudomonas Exotoxin for vaccination – inserts of 14 or 26 amino acids were used from MN or a Thai E strain, constrained by disulfide bond – sera from vaccinated rabbit were reactive with strain-specific gp120 – administration to mucosal surfaces elicits IgA. FitzGerald *et al.* [1998]

**No.** 442

**MAb ID** polyclonal

**HXB2 Location** gp160 (297–330)

**Author Location** Env (303–335 LAI)

**Epitope** TRPNNNTRKSIHIGPGRAFYTGEIIGDIRQAH

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* V3 *Adjuvant:* QS21

**Species (Isotype)** human (IgG)

**Ab Type** gp120 V3

**References** Pialoux *et al.* 2001

- 28 subjects were vaccinated with six HIV-1 peptides that were selected to be particularly rich in CTL epitopes, presented in lipopeptides with or without adjuvant QS21 – HIV-specific Ab responses were detected in 25/28 (89%), proliferative in 19/28 (79%), and CTL in 13/24 (54%) of testable volunteers – 14/28 had non-neutralizing Ab responses to this peptide (E), 7/24

had proliferative responses, and multiple CTL responses were detected. Pialoux *et al.* [2001]

**No.** 443

**MAb ID** MO97/V3

**HXB2 Location** gp160 (299–308)

**Author Location** gp120 (299–308 IIIB)

**Epitope** PNNNTRKSIR

**Neutralizing** no

**Immunogen** in vitro stimulation or selection

**Species (Isotype)** human (IgM)

**Ab Type** gp120 V3

**References** Gorny & Zolla-Pazner 2004; Ohlin *et al.* 1992

**Keywords** review

- M097/V3: Review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains; a subset can also neutralize some primary isolates. The three IgMs, M096, M097, and M099, are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- M097: Generated through *in vitro* stimulation of uninfected-donor lymphocytes with rpB1 (IIIB Env 286–467) Ohlin *et al.* [1992]

**No.** 444

**MAb ID** polyclonal

**HXB2 Location** gp160 (299–331)

**Author Location** gp120 (306–338 BH10)

**Epitope** PNNNTRKSIRIQRGPGRAFVTIGKIGNMRQAH

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BH10

**Species (Isotype)** rabbit (IgG)

**Ab Type** gp120 V3

**References** Neurath & Strick 1990

- 21 V3 loop variant peptides spanning this region were tested and serological cross-reactivity correlated with divergence. Neurath & Strick [1990]

**No.** 445

**MAb ID** 55/11

**HXB2 Location** gp160 (300–315)

**Author Location** gp120 (300–315)

**Epitope** NNNTRKRIRIQRGPGR?

**Neutralizing**

**Immunogen**

**Species (Isotype)**

**Ab Type** gp120 V3

**References** Peet *et al.* 1998

- 55/11: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, and anti-V3 MAb 55/11 binding was abrogated by V3 serine substitutions in the V3 loop – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

**No.** 446

**MAb ID** 8/38c (8/38/1c, 8/38)

**HXB2 Location** gp160 (300–315)  
**Author Location** gp120 (300–315 HXB10)  
**Epitope** NNNTRKRIRIQRGPGR  
**Neutralizing L**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)** rat (IgG2a)  
**Ab Type** gp120 V3  
**Research Contact** C. Dean and C. Shotton, Institute for Cancer Research, Surrey, UK  
**References** Holl *et al.* 2006a; Peet *et al.* 1998; Parren *et al.* 1998a; Jeffs *et al.* 1996; Sattentau & Moore 1995; McKeating *et al.* 1992a

**Keywords** dendritic cells, neutralization

- 8/38c: UK Medical Research Council AIDS reagent: ARP3039.
- 8/38: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 8/38c: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- 8/38c: Called 8/38/1c: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, and anti-V3 MAb 8/38c binding was only diminished by V3 serine substitutions C-term to the tip of the loop – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 8/38c: Deletion of the V1V2 regions did not affect anti-V3 Abs ability to bind when compared to intact rec gp120. Jeffs *et al.* [1996]
- 8/38c: Binds equally well to monomer and oligomer, less rapid association rate than other anti-V3 antibodies, and an associated less potent neutralization of lab strains. Sattentau & Moore [1995]
- 8/38c: Binds to virion gp120 and neutralizes only in the presence of sCD4. McKeating *et al.* [1992a]

**No.** 447

**MAb ID** 8/64b

**HXB2 Location** gp160 (300–315)  
**Author Location** gp120 (300–315 HXB10)  
**Epitope** NNNTRKRIRIQRGPGR  
**Neutralizing L**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)** rat (IgM)  
**Ab Type** gp120 V3  
**References** Holl *et al.* 2006a; Peet *et al.* 1998; McKeating *et al.* 1992a

**Keywords** dendritic cells, neutralization

- 8/64b: UK Medical Research Council AIDS reagent: ARP3036.

- 8/64b: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 8/64b: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, and anti-V3 MAb 8/64b binding was abrogated by V3 serine substitutions C-term to the tip of the loop – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 8/64b: Binds to virion gp120 and neutralizes only in the presence of sCD4. McKeating *et al.* [1992a]

**No.** 448

**MAb ID** polyclonal

**HXB2 Location** gp160 (300–321)  
**Author Location** gp120  
**Epitope** NYNKRKRHIIGPGRAFYTTK  
**Neutralizing L**  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* peptide *HIV component:* V3  
**Species (Isotype)** human  
**Ab Type** gp120 V3  
**References** Bartlett *et al.* 1998

- V3 peptide vaccine (MN, RF, EV91, and Can0A) with a C4 helper T cell epitope were used to vaccinate HLA-B7 HIV-infected patients – V3 Ab levels and the anti-HIV proliferative response, but no decrease in HIV-1 RNA levels or increase in CD4 levels was observed. Bartlett *et al.* [1998]

**No.** 449

**MAb ID** polyclonal

**HXB2 Location** gp160 (300–321)  
**Author Location** gp120  
**Epitope** NYNKRKRHIIGPGRAFYTTK  
**Neutralizing**  
**Immunogen** HIV-1 exposed seronegative  
**Species (Isotype)** human (IgA)  
**Ab Type** gp120 V3  
**References** Kaul *et al.* 1999

- HIV-1 Env-specific mucosal IgA found in genital track of 16/21 HIV-1 resistant chronically exposed Kenyan sex workers – 11/21 had detectable Th responses. Kaul *et al.* [1999]

**No.** 450

**MAb ID** polyclonal

**HXB2 Location** gp160 (300–322)  
**Author Location** gp120 (IIIB)  
**Epitope** CNNTRKSIRIQRGPGRAFVTIGK  
**Neutralizing L**  
**Immunogen**  
**Species (Isotype)** guinea pig (IgG)  
**Ab Type** gp120 V3  
**Research Contact** D. Bolognesi and T. Matthews, Duke University  
**References** Allaway *et al.* 1993

- Synergy with combinations of CD4-based molecules in inhibition of HIV-1 Env mediated cell fusion. Allaway *et al.* [1993]

No. 451

**MAb ID** polyclonal (VEI3)**HXB2 Location** gp160 (300–328)**Author Location** Env**Epitope** NNNTRKSIRIGPGRAFYTGDIGNIRQ**Neutralizing****Immunogen** HIV-1 infection**Species (Isotype)** human**Ab Type** gp120 V3**References** Carlos *et al.* 1999

- Antibody response to the epitopes in a vaccine construct (VEI) containing peptides from 5 hypervariable regions of gp120 was detected in the sera of HIV-1 positive subjects, including sera from 6 non-subtype B infections – serum samples from San Francisco, Canada and Puerto Rico cohort showed presence of antibodies against all five VEI hypervariable regions, but most consistently against the V3 region peptide NNNTRKSIRIGPGRAFYTGDIGNIRQ. Carlos *et al.* [1999]

No. 452

**MAb ID** 9284 (NEA 9284)**HXB2 Location** gp160 (301–312)**Author Location** gp120 (307–318 IIIB)**Epitope** NNTRKSIRIQRG**Neutralizing** L**Immunogen** vaccine*Vector/Type:* inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1**Species (Isotype)** mouse (IgG1)**Ab Type** gp120 V3**Research Contact** Dupont de Nemours, Les Ulis, France or Wilmington, Delaware

**References** Schonning *et al.* 1998; Parren *et al.* 1998a; Binley *et al.* 1997a; Cao *et al.* 1997b; Poignard *et al.* 1996a; Moore & Sodroski 1996; Fontenot *et al.* 1995; VanCott *et al.* 1995; Sattentau & Moore 1995; Sorensen *et al.* 1994; Okada *et al.* 1994; Cook *et al.* 1994; Thali *et al.* 1994; VanCott *et al.* 1994; Thali *et al.* 1993; Trujillo *et al.* 1993; Moore *et al.* 1993b; Sattentau *et al.* 1993; McKeating *et al.* 1992a; Wyatt *et al.* 1992; Sattentau & Moore 1991; Skinner *et al.* 1988a; Skinner *et al.* 1988b

- 9284: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- 9284: In a study of the influence of the glycan at position 306 of the V3 loop on MAb recognition, 9284 was found to have an inaccessible epitope on the oligomeric form of Env and anti-V3 MAbs were found to neutralize an HIV-BRU mutant virus that lacks the V3 loop glycan more efficiently than HIV-BRU. Schonning *et al.* [1998]
- 9284: Virus with the V1-V2 loop deleted was viable and more susceptible to neutralization by CD4i MAb 17b, and anti-V3 MAbs 1121, 9284, and 110.4, but not to and CD4BS MAb F105 or sCD4. Cao *et al.* [1997b]

- 9284: Binds V3 loop – anti-C1 MAbs 133/290 and 135/9 enhance binding – reciprocal binding inhibition of other anti-V3 MAbs. Moore & Sodroski [1996]
- 9284: V3 MAbs 9284, BAT123, 110.5, and 110.I could each significantly increase gp120 dissociation from virus, mimicking sCD4, and expose the gp41 epitope for MAb 50-69, in contrast to anti-V2 MAbs. Poignard *et al.* [1996a]
- 9284: Binds equally well to monomer and oligomer, rapid association and potent neutralization of lab strains – neutralizes cell-free virus Hx10. Sattentau & Moore [1995]
- 9284: Used to monitor HIV-1 Env expression in infected H9 cells, binds native and reduced gp120s similarly. VanCott *et al.* [1995]
- 9284: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – this MAb can inhibit gp120 binding to GalCer *in vitro*. Cook *et al.* [1994]
- 9284: Binding domain aa 301-310: TRKSIRIQRG – mutations in the V3 loop from basic residues can destroy virus infectivity and syncytium formation: R306T, R309T and R313G can also reduce binding of V3 MAbs with two different binding sites: 9284 and 0.5beta – called NEA9284. Okada *et al.* [1994]
- 9284: Did not neutralize infection of HIV/HTLV-I pseudotype. Sorensen *et al.* [1994]
- 9284: gp41 mutation that confers resistance to neutralization by anti-CD4 binding site antibodies does not reduce neutralizing efficiency of this V3 region MAb. Thali *et al.* [1994]
- 9284: Does not bind MN gp120, just IIIB. VanCott *et al.* [1994]
- 9284: Inhibits C4 region antibodies (G3-299, G3-519) which have conformational requirements. Moore *et al.* [1993b]
- 9284: Increased binding in the presence of sCD4. Sattentau *et al.* [1993]
- 9284: Peptide RIQRGPGRAFVTIGKIGNMRQA – Reacts with three human brain proteins of 35, 55, 110 kd – called NEA-9284. Trujillo *et al.* [1993]
- 9284: Single amino acid substitutions in the C4 region (427 W/V or W/S) or at the base of the V3 loop (298 R/G) can significantly increase binding and neutralization – position 427 is also important for CD4 binding and anti-CD4 binding site MAbs. Wyatt *et al.* [1992]
- 9284: Two fold increase in binding to gp120 in the presence of bound sCD4. Sattentau & Moore [1991]
- 9284: IIIB type-specific binding and neutralization. Skinner *et al.* [1988b]

No. 453

**MAb ID** polyclonal**HXB2 Location** gp160 (301–325)**Author Location** gp120 (IIIB)**Epitope** NNTRKSIRIQRGPGRAFVTIGKIGN**Neutralizing** L**Immunogen** vaccine*Vector/Type:* peptide *Strain:* B clade IIIB  
*Adjuvant:* Cholera toxin (CT)**Species (Isotype)** mouse (IgA)**Ab Type** gp120 V3**References** Bukawa *et al.* 1995

- Polyclonal secretory IgA antibody raised by mucosal immunization is able to neutralize IIB, SF2, and MN – HIV-1 neutralization may be due to V3, CD4 or HPG30 component of the multicomponent peptide immunogen. Bukawa *et al.* [1995]

No. 454

- MAb ID** polyclonal  
**HXB2 Location** gp160 (301–325)  
**Author Location** gp120 (IIB)  
**Epitope** NNTRKSIRIQRGPGRAFVTIGKIGN  
**Neutralizing L**  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade IIB  
*HIV component:* Env, Rev  
**Species (Isotype)** mouse (IgA22a)  
**Ab Type** gp120 V3  
**References** Sasaki *et al.* 1998
- An anti-env response was sought, and co-expression of Rev was required – intramuscular versus nasal vaccination with DNA vaccine with a QS21 adjuvant was studied – QS21 enhanced the IgG2a response mediated via Th1 cytokines IFN $\gamma$  and IL-2. Sasaki *et al.* [1998]

No. 455

- MAb ID** polyclonal  
**HXB2 Location** gp160 (302–317)  
**Author Location** Env (B consensus)  
**Epitope** NTRKSIHIGPGRAF  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 V3  
**References** Morris *et al.* 2001b
- Ab responses before HAART therapy and after one year of therapy were measured in 8 individuals that were classified HAART successes, and 10 patients who were classified as HAART failures – V3 peptide antibody binding titers to the B-consensus and MN and SF2 variants, and neutralization of HIV-1 MN and four subtype B clinical isolates were tested – subjects with strong anti-V3 and NAb humoral immune responses before starting HAART were more likely to achieve sustained viral suppression to <500 copies RNA/ml on HAART – HIV-specific Ab responses declined after 1 year of successful viral suppression on HAART. Morris *et al.* [2001b]

No. 456

- MAb ID** polyclonal  
**HXB2 Location** gp160 (302–318)  
**Author Location** Env  
**Epitope** NTRKSIHIGPGRAFY  
**Neutralizing L P**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 V3  
**References** Bongertz *et al.* 2001

- Non-transmitting mothers had an increased frequency of high neutralizing plasma Ab titers against HIV-1 MN (1:50 dilution, >90% neutralization, 33/88 pregnant women), compared to plasma from transmitting mothers (0/8 pregnant women) – non-transmitting mothers also had more potent neutralization against primary isolates from transmitting mothers, but neutralization of autologous virus was comparable for non-transmitting (7/13) and transmitting mothers (2/4) Bongertz *et al.* [2001]

No. 457

- MAb ID** MAG 109  
**HXB2 Location** gp160 (302–321)  
**Author Location** gp120 (302–321 BH10)  
**Epitope** NTRKSIRIQRGPGRAFVTIG  
**Neutralizing L**  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 V3  
**References** Kang *et al.* 1994
- MAG 109: Binds a V3 loop peptide – sensitive to both V3 loop mutations and a mutation at the base of the V1/V2 loop structure (120/121 VK/LE) Kang *et al.* [1994]

No. 458

- MAb ID** MAG 49 (#49)  
**HXB2 Location** gp160 (302–321)  
**Author Location** gp120 (302–321 BH10)  
**Epitope** NTRKSIRIQRGPGRAFVTIG  
**Neutralizing L**  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 V3  
**References** Moore & Sodroski 1996; Kang *et al.* 1994
- MAG 49: Called #49 in this text. Binding enhanced by anti-C1 MAbs 133/290, 135/9, and by many anti-CD4 binding site MAbs – reciprocal enhancement of some anti-V2 MAbs – reciprocal binding inhibition of anti-V3 MAbs. Moore & Sodroski [1996]
  - MAG 49: Binds a V3 loop peptide – sensitive to both V3 loop mutations and a mutation at the base of the V1/V2 loop structure (120/121 VK/LE) Kang *et al.* [1994]

No. 459

- MAb ID** MAG 53  
**HXB2 Location** gp160 (302–321)  
**Author Location** gp120 (302–321 BH10)  
**Epitope** NTRKSIRIQRGPGRAFVTIG  
**Neutralizing L**  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 V3  
**References** Kang *et al.* 1994

- MAG 53: Binds a V3 loop peptide – sensitive to both V3 loop mutations and a mutation at the base of the V1/V2 loop structure (120/121 VK/LE) Kang *et al.* [1994]

No. 460

**MAb ID** MAG 56

**HXB2 Location** gp160 (302–321)

**Author Location** gp120 (302–321)

**Epitope** NTRKSIRIQRGPGRAFTIG

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* sCD4-gp120 complex *Strain:*

B clade HXB2 *HIV component:* gp120

**Species (Isotype)** mouse

**Ab Type** gp120 V3

**References** Kang *et al.* 1994

- MAG 56: Binds a V3 loop peptide – sensitive to both V3 loop mutations and a mutation at the base of the V1/V2 loop structure (120/121 VK/LE) Kang *et al.* [1994]

No. 461

**MAb ID** 1334-D (1334, 1334D)

**HXB2 Location** gp160 (303–307)

**Author Location** gp120 (HIV451)

**Epitope** TRTSV

**Subtype** CRF01\_AE

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Gorny *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a

**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1334-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 1334-D: Called 1334. V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using HIV451 gp120. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 1334-D: Called 1334 – binds to V3 peptides from MN, SF2, NY5, RF, and CDC4 strains as well as x-reactivity with peptides from A, C, D, F, G, and H subtypes – was suggested to be IgG1λ here – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and

C5 tended to favor the monomer – V3 MAbs 447-52D, 838-D, and 1334 bound with a 7-10 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons**)

- 1334-D: Called 1334D – A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 1334D showed intermediate cross-reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1334-D: This MAb was selected using oligomeric gp160 from HIV451. Zolla-Pazner *et al.* [1999a] (**antibody generation**)
- 1334-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)

No. 462

**MAb ID** 1324-E (1324E)

**HXB2 Location** gp160 (303–308)

**Author Location** Env (subtype CRF01)

**Epitope** TRTSVR

**Subtype** CRF01\_AE

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

**References** Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1998

**Keywords** antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1324-E: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 1324-E: Called 1324E – A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 1324E showed poor cross-reactivity, and was the only MAb tested that was derived from a non-B clade infected patient, an E clade infection was the source of 1324E. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1324-E: E clade stimulated MAb did not cross-react with B clade peptides nor did B clade derived peptides with an E clade V3 loop, but both E and B clade stimulated Abs can cross-react with some peptides from other clades – this Ab showed strong binding to several E, A and F peptides, one C peptide, and no reactivity with B peptides and most D peptides. Zolla-Pazner *et al.* [1999a] (**subtype comparisons**)

- 1324-E: MAb reacted with peptides from E clade, while B clade derived MAbs could not. Zolla-Pazner *et al.* [1999b] (**subtype comparisons**)
- 1324-E: A human MAb was derived from an HIV-1 E clade infection from a US service man who had served in Thailand, selected with the consensus V3 peptide from clade E – cross-reactive with V3 peptides, and gp120 from E, C and A clades, as well as cells infected with a C-clade primary isolate, but not with B and D clade V3 peptides or rgp120 – neutralizes E clade virus adapted for growth in H9 cells, but not 5 primary E clade isolates, including the autologous isolate – kinetic parameters were measured, 1324E was comparable to 447-52D. Gorny *et al.* [1998] (**antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 463

Mab ID polyclonal

HXB2 Location gp160 (303–319)

Author Location gp120 (subtype C)

Epitope CKRKIHIGPGQAFYT

Subtype C

Neutralizing

Immunogen vaccine

*Vector/Type:* peptide in ISCOM, peptide in liposome *HIV component:* V3 *Adjuvant:* Immune stimulating complexes (ISCOM)

Species (Isotype) mouse (IgG2a, IgG2b)

Ab Type gp120 V3

References Ahluwalia *et al.* 1997

- A V3 loop peptide modified to resemble an Indian form (GPGQ) was incorporated into ISCOMS (immune stimulating complexes) or liposomes, and used to immunize mice – the IgG2a/IgG2b antibody response was enhanced by the presentation in the ISCOM suggestive of a Th1 response. Ahluwalia *et al.* [1997]

No. 464

Mab ID MO99/V3

HXB2 Location gp160 (304–308)

Author Location gp120 (304–308 IIIB)

Epitope RKSIR

Neutralizing no

Immunogen *in vitro* stimulation or selection

Species (Isotype) human (IgM)

Ab Type gp120 V3

References Gorny & Zolla-Pazner 2004; Ohlin *et al.* 1992

**Keywords** antibody binding site definition and exposure, antibody generation

- MO99/V3: Review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains; a subset can also neutralize some primary isolates. The three IgMs, M096, M097, and M099, are non-neutralizing. Gorny & Zolla-Pazner [2004]
- MO99: Generated through *in vitro* stimulation of uninfected-donor lymphocytes with rpB1 (IIIB Env 286–467) Ohlin *et al.* [1992] (**antibody binding site definition and exposure, antibody generation**)

No. 465

Mab ID C311E

HXB2 Location gp160 (304–313)

Author Location gp120 (309–316 MN)

Epitope RKRIHIGP

Neutralizing L

Immunogen HIV-1 infection

Species (Isotype) chimpanzee (IgG1)

Ab Type gp120 V3

References Alsmadi & Tilley 1998; Warrier *et al.* 1996

- C311E: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – C311E bound and directed lysis against all four strains. Alsmadi & Tilley [1998]
- C311E: Chimps were infected with HIV-1 IIIB, and this resulting MAb gave synergistic neutralization of HIV-1 when combined with anti-V2 MAb C108G. Warrier *et al.* [1996]

No. 466

Mab ID 907

HXB2 Location gp160 (304–314)

Author Location gp120 (309–318)

Epitope RKSIRIQRGPG

Neutralizing L

Immunogen vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* gp160

Species (Isotype) mouse (IgG1κ)

References Pincus *et al.* 1996; Pincus *et al.* 1991; Pincus *et al.* 1989; Chesebro & Wehrly 1988

- 907: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996]
- 907: Epitope sequence is based on database count of a specified location – 924-RAC immunotoxin is IIIB strain-specific. Pincus *et al.* [1991]
- 907: Coupled to ricin A chain (RAC), MAb 907 inhibited protein synthesis and cell growth in HIV-infected cells. Pincus *et al.* [1989]
- 907: Strain specific binding, and neutralization of only the LAV strain. Chesebro & Wehrly [1988]

No. 467

Mab ID 924

HXB2 Location gp160 (304–314)

Author Location gp120 (309–318 IIIB)

Epitope RKSIRIQRGPG

Neutralizing

Immunogen vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* gp160

Species (Isotype) mouse (IgG1κ)

Ab Type gp120 V3

References Pincus *et al.* 1998; Pincus *et al.* 1996; Cook *et al.* 1994; Pincus *et al.* 1993; Pincus & McClure 1993; Pincus *et al.* 1991; Chesebro & Wehrly 1988

- 924: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996]
- 924: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – this MAb can inhibit gp120 binding to GalCer *in vitro*. Cook *et al.* [1994]
- 924: MAb was coupled to ricin A chain (RAC) – immunotoxin efficacy was not significantly decreased by sCD4, although the efficacy of gp41 MAb immunotoxins *in vitro* increased 30-fold by sCD4. Pincus & McClure [1993]
- 924: Ab response in IIIB lab workers was compared to gp160 LAI vaccine recipients – MAb 924 was used as a control – infected lab workers and a vaccinia gp160 vaccine had strong V3 MAb response, but alum absorbed rec gp160 did not generate anti-V3 response. Pincus *et al.* [1993]
- 924: Epitope sequence is based on database count of a specified location – 924-RAC immunotoxin is IIIB strain-specific. Pincus *et al.* [1991]
- 924: HIV IIIB strain specific. Chesebro & Wehrly [1988]

No. 468

MAB ID polyclonal

HXB2 Location gp160 (304–318)

Author Location gp120 (304–318 LAI)

Epitope RKSIRIQRGPGRFV

Subtype B

Neutralizing

Immunogen *in vitro* stimulation or selection

Species (Isotype) human (IgG, IgM)

Ab Type gp120 V3

References Chin *et al.* 1995

- Mimicking the humoral immune response *in vitro* supports isotype switching – human IgG MAbs were generated from naive donors. Chin *et al.* [1995]

No. 469

MAB ID polyclonal

HXB2 Location gp160 (304–318)

Author Location gp120 (304–318 LAI)

Epitope RKSIRIQRGPGRFV

Subtype B

Neutralizing

Immunogen vaccine

Vector/Type: peptide Strain: B clade LAI

Species (Isotype) human (IgG, IgM)

Ab Type gp120 V3

References Zafiroopoulos *et al.* 1997

- IgG to IgM isotype switching in response to primary and secondary peptide vaccinations was studied – the immunogen contained a V3 loop fragment and a tetanus toxin helper epitope. Zafiroopoulos *et al.* [1997]

No. 470

MAB ID polyclonal

HXB2 Location gp160 (304–318)

Author Location gp120 (NY5)

Epitope KKGIAIGPGRTRY

Neutralizing

**Immunogen**

Species (Isotype) (IgM)

Ab Type gp120 V3

References Metlas *et al.* 1999a; Metlas *et al.* 1999b

- Auto-Abs that react with the V3 loop of NY5 are present in the sera of HIV- individuals, and are predominantly IgM. Metlas *et al.* [1999b]

No. 471

MAB ID D19

HXB2 Location gp160 (304–320)

Author Location gp120 (V3) (MN)

Epitope RKRIHIGPGRFYTT

Subtype A, B, F

Neutralizing yes

Immunogen vaccine

Vector/Type: protein Strain: B clade BH8

HIV component: gp140

Species (Isotype) mouse (IgG)

Ab Type gp120 CD4i, gp120 V3

Research Contact Paolo Lusso, Human Virology, San Raffaele Scientific Institute, Milan, Italy. paolo@hsr.it

References Lusso *et al.* 2005

Keywords antibody binding site definition and exposure, antibody generation, subtype comparisons, variant cross-recognition or cross-neutralization

- D19: The epitope for D19 is conserved and embedded in V3. D19 is unique because for R5 viruses, it was cryptic and did not bind without exposure to sCD4, but for X4 and R5X4 isolates it was constitutively exposed. It had a similar overlapping binding region with MAbs 447-52D, B4e8, and 268-D, but different reactivity patterns and fine specificity; D19 binding to monomeric gp120 was independent of sCD4, the dependence was only seen in the context of native oligomeric Env. D19 reacted with 23/29 B clade Envs, but to only 2/14 viruses from other clades: one A and one F, but no C, D or E clade strains. D19 can neutralize X4 and R5X4 isolates, but could only neutralize R5 isolates in the presence of sCD4. The authors suggest that a more exposed V3 loop may facilitate CXCR4 coreceptor usage, but that this phenotype is limited *in vivo* by neutralizing antibodies until the onset of progressive disease. Lusso *et al.* [2005] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 472

MAB ID 10F10

HXB2 Location gp160 (304–320)

Author Location gp120 (MN)

Epitope RKRIHIGPGRFYTT

Neutralizing L

Immunogen vaccine

Vector/Type: peptide Strain: B clade MN

HIV component: gp120

Species (Isotype) mouse (IgG1)

Ab Type gp120 V3

References Duarte *et al.* 1994



- 2C4: Putative epitope lies within IHIGPGRAFYT – generated by multi-epitope polypeptide immunization – recognize MN and SC (TRSIHIGPGRAFYT) peptides, lower affinity for SF2. Duarte *et al.* [1994]

No. 473

**MAb ID** 2C4

**HXB2 Location** gp160 (304–320)

**Author Location** gp120 (MN)

**Epitope** RKRIHIGPGRAFYT

**Neutralizing** L (MN)

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade MN

**Species (Isotype)** mouse (IgG2a)

**Ab Type** gp120 V3

**References** Duarte *et al.* 1994

- 2C4: Putative epitope lies within IHIGPGRAFYT – neutralizes MN, not IIB and SF2 – generated by multi-epitope polypeptide immunization – recognize MN and SC (TRSIHIGPGRAFYT) peptides, lower affinity for SF2. Duarte *et al.* [1994]

No. 474

**MAb ID** 412-D (412-10D, 412, 412D)

**HXB2 Location** gp160 (304–320)

**Author Location** gp120 (MN)

**Epitope** RKRIHIGPGRAFYT

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Nyambi *et al.* 1998; Gorny *et al.* 1998; Fontenot *et al.* 1995; VanCott *et al.* 1994; Spear *et al.* 1993; Gorny *et al.* 1993

**Keywords** antibody binding site definition and exposure, binding affinity, complement, kinetics, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 412-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 412-D: Called 412: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

- 412-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 412-D showed limited reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 412-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
- 412-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 391.5, 412 and 418, all selected with MN V3 peptide – the core amino acids HIGPGR tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 412-D: Kinetic parameters were measured, and the association rates were similar, but dissociation rate constants were quite variable for V3 MAbs, 412-D has a relatively fast dissociation, thus low affinity among V3 MAbs. Gorny *et al.* [1998] (**kinetics**)
- 412-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – 412-D was bound only to B clade virions and to D clade MAL. Nyambi *et al.* [1998] (**subtype comparisons**)
- 412-D: Called 412 – The tip of the V3 loop was presented in a mucin backbone – higher valency correlates with higher affinity constant. Fontenot *et al.* [1995] (**vaccine antigen design, binding affinity**)
- 412-D: Called 412-10D – relatively rapid dissociation and weak homologous neutralization. VanCott *et al.* [1994] (**binding affinity**)
- 412-D: Neutralizes MN, does not bind SF2 or HXB2 – not reactive with hexa or heptapeptides by Pepsan. Gorny *et al.* [1993] (**variant cross-recognition or cross-neutralization**)
- 412-D: Mediated deposition of complement component C3 on HIV infected cells, enhanced by second Ab binding, rabbit anti-human IgG. Spear *et al.* [1993] (**complement**)

No. 475

**MAb ID** polyclonal

**HXB2 Location** gp160 (304–320)

**Author Location** gp120 (MN)

**Epitope** RKRIHIGPGRAFYT

**Neutralizing** L (MN ALA-1)

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 V3

**References** Spear *et al.* 1994

- 40% of antibody in serum that can bind to native viral proteins on MN-infected cells can be blocked by the peptide RKRIHIGPGRAFYT, which can also block 75-95% of the complement activation on HIV infected cells. Spear *et al.* [1994]

No. 476

**MAb ID** CGP 47 439

**HXB2 Location** gp160 (304–322)

**Author Location** gp120

**Epitope** RKRIIRIQRGPGRFVTIG?

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120

**Species (Isotype)** human  
**Ab Type** gp120 V3

**References** Jacobson 1998; Gauduin *et al.* 1998; Gunthard *et al.* 1994; Safrit *et al.* 1993; Liou *et al.* 1989

- CGP 47 439: Post-exposure passive transfer of murine BAT123 can confer protection to hu-PBL-SCID mice challenged with HIV-1 LAI – this protection is not elicited by CGP 47 439, suggesting that the protection is mediated by complement – the protective ability of BAT123 is lost when mice were treated with cobra venom factor, which inactivates serum complement – in this circumstance complement activation provided a protective advantage. Gauduin *et al.* [1998]
- CGP 47 439: Review of passive immunotherapy, summarizing Gunthard *et al.* [1994] in relation to other studies Jacobson [1998]. Gunthard *et al.* [1994]; Jacobson [1998]
- CGP 47 439: Phase I/IIA clinical trial studying multidose tolerability, immunogenicity and pharmacokinetic responses – GP 47 439 was well tolerated, serum t<sub>1/2</sub> was 8-16 days, and a virus burden reduction was noted in some patients. Gunthard *et al.* [1994]
- CGP 47 439: passive transfer to Hu-PBS-SCID mice confers protection against challenge with homologous cell-free virus – CGP 47 439 is a BAT123-human Ig chimera. Safrit *et al.* [1993]

**No.** 477  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (304–322)  
**Author Location** (MN)  
**Epitope** RKRIHIGPGRAFYTTKN  
**Subtype** multiple  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 V3

**References** Cheingsong-Popov *et al.* 1992

- The Ab response of 829 HIV-1 infected subjects from eight geographic areas to a set of different V3 peptides was determined by ELISA and cross-inhibition studies – the Ab binding pattern was highly variable, depended on the geographic origin of the sample – 297 sera were tested in a neutralization assay – there was a correlation between Ab binding to the MN V3 loop and MN neutralizing titer, but with neutralization of IIIB or CBL-4. Cheingsong-Popov *et al.* [1992]

**No.** 478  
**MAb ID** 178.1 (178.1.1)  
**HXB2 Location** gp160 (305–309)  
**Author Location** gp120 (305–309 BH10)  
**Epitope** KSiRI  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* Env

**Species (Isotype)** mouse (IgG2a)  
**Ab Type** gp120 V3

**Research Contact** C. Thiriart, Smith Kline and MRC AIDS reagent project

**References** Holl *et al.* 2006a; Cook *et al.* 1994; Moore & Ho 1993; Back *et al.* 1993; Thiriart *et al.* 1989

**Keywords** dendritic cells, neutralization

- 178.1: UK Medical Research Council AIDS reagent: ARP331.
- 178.1.1: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 178.1: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – this MAb can inhibit gp120 binding to GalCer *in vitro* – binding of GalCer to gp120 inhibited but did not completely block MAb binding. Cook *et al.* [1994]
- 178.1: gp41 amino acid substitutions 668 (N/S) and 675 (I/M) in gp41 interfere with 5023s neutralization potency, region 662-675 is ELDKWANLWNWFNI. Back *et al.* [1993]
- 178.1: Called 178.1.1 – conformational, does not bind well to denatured gp120. Moore & Ho [1993]
- 178.1: Reacts to gp120 and gp160 in RIPA EIA and immunoblot. Thiriart *et al.* [1989]

**No.** 479

**MAb ID** 257-D (257, 257-2-D-IV, 257-D-IV, 257, 257-2D, 257D, ARP3023)

**HXB2 Location** gp160 (305–309)

**Author Location** gp120 (MN)

**Epitope** KRIHI

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1λ)

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mercrc6.med.nyu) (NYU Med. Center)

**References** Holl *et al.* 2006a; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; Vella *et al.* 2002; York *et al.* 2001; Park *et al.* 2000; Nyambi *et al.* 2000; Oggioni *et al.* 1999; Beddows *et al.* 1999; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Stamatatos & Cheng-Mayer 1998; Gorny *et al.* 1998; Yang *et al.* 1998; LaCasse *et al.* 1998; Hioe *et al.* 1997b; Hill *et al.* 1997; Stamatatos *et al.* 1997; Schutten *et al.* 1997; Schutten *et al.* 1996; Wisniewski *et al.* 1996; Fontenot *et al.* 1995; Schutten *et al.* 1995b; Schutten *et al.* 1995a; Zolla-Pazner *et al.* 1995; D'Souza *et al.* 1995; Stamatatos & Cheng-Mayer 1995; VanCott *et al.* 1994; D'Souza *et al.* 1994; Spear *et al.* 1993; Cavacini *et al.* 1993a; Gorny *et al.* 1993; Karwowska *et al.* 1992b; D'Souza *et al.* 1991; Gorny *et al.* 1991

- Keywords** antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, assay development, binding affinity, co-receptor, complement, dendritic cells, enhancing activity, kinetics, neutralization, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization
- 257-D: UK Medical Research Council AIDS reagent: ARP3023.
  - 257-D: NIH AIDS Research and Reference Reagent Program: 1510.
  - 257-D IV: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
  - 257-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
  - 257-D: Called 257: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides do not show as much ability to neutralize as V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 257 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
  - 257-D: Called ARP3023: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs. Vella *et al.* [2002] (**assay development**)
  - 257-D: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**variant cross-recognition or cross-neutralization**)
  - 257-D: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001]
  - 257-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 257-D showed intermediate reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
  - 257-D: Called 257D – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
  - 257-D: rgp120 derived from a R5X4 subtype B virus, HIV-1 W61D, was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs – 257-D bound rgp120 W61D but could only neutralize the W61D isolate following T-cell line adaptation. Beddows *et al.* [1999] (**vaccine antigen design, variant cross-recognition or cross-neutralization, vaccine-specific epitope characteristics**)
  - 257-D: Study of a live-vector mucosal vaccine that expresses HIV-1 V3 domains using the bacterium *Streptococcus gordonii* which can express heterologous Ag and can colonize the oral cavity and vagina of mice – 268-D and 257-D recognized *S. gordonii* expressing the V3 domain of MN – the vaccine stimulated V3-specific IgG2a in mice. Oggioni *et al.* [1999] (**vaccine antigen design**)
  - 257-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
  - 257-D: MAb peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
  - 257-D: Kinetic parameters were measured, and the association rates were similar, but dissociation rate constants were quite variable for V3 MAbs, 257-D has a slow dissociation, thus the highest affinity among V3 MAbs. Gorny *et al.* [1998] (**kinetics, binding affinity**)
  - 257-D: A T-cell line-adapted (TCLA) derivative of SI primary isolate 168P acquired the ability to be neutralized by anti-V3 MAbs – the primary isolate could use either CCR5 or CXCR4, and was not neutralized when infection was directed via either pathway, however the TCLA derivative uses CXCR4 only and is neutralized. LaCasse *et al.* [1998] (**co-receptor, variant cross-recognition or cross-neutralization**)
  - 257-D: Called 257D – deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V1 or V2 did not enable neutralization by V3 MAbs 391-95D or 257D. Stamatatos & Cheng-Mayer [1998] (**vaccine antigen design, subtype comparisons**)

- 257-D: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998] (**assay development**)
  - 257-D: Called 257 – gp120 can inhibit MIP-1alpha from binding to CCR5, but this inhibitory effect is blocked by pre-incubation of gp120 with three anti-V3 MAbs: 447, 257, 1027 – MAb 670 which binds in the C5 region had no effect. Hill *et al.* [1997] (**antibody binding site definition and exposure, co-receptor**)
  - 257-D: Neutralized (>90%) an SI-env chimeric virus and enhanced (>200%) an NSI-env chimeric virus. Schutten *et al.* [1997] (**enhancing activity, variant cross-recognition or cross-neutralization**)
  - 257-D: Binds less extensively than MAb 391-95D on the surface of HIV-1 isolates SF162 and SF128A – neutralizes less potently than 391-95D – stronger neutralization of primary macrophage targets than PBMC. Stamatatos *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
  - 257-D: IIIB neutralizing MAbs *in vitro* fail to neutralize in a mouse model *in vivo*. Schutten *et al.* [1996]
  - 257-D: 257-D is V H5 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996] (**antibody sequence variable domain**)
  - 257-D: Called 257-D-IV – could neutralize MN and closely related JRCSF, but not 2 B subtype and 1 D subtype primary isolates in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 257-D: Only inhibition of SI phenotype virus, and strong enhancement of NSI phenotype chimeric viruses, that incorporated different envs from the same donor. Schutten *et al.* [1995a] (**enhancing activity, variant cross-recognition or cross-neutralization**)
  - 257-D: Comparable affinity for SI and NSI viruses, in contrast to MAb MN215. Schutten *et al.* [1995b] (**variant cross-recognition or cross-neutralization**)
  - 257-D: The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – V3 loop epitopes were less accessible to Ab binding on the virion surface than in the gp120 monomer, particularly for macrophage-tropic isolates SF162 and SF128a, relative to T-cell tropic SF2 – sCD4 association with gp120 better revealed this V3 epitope on TCLA SF2 and dual tropic (MU3) viruses than on macrophage tropic isolates. Stamatatos & Cheng-Mayer [1995] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 257-D: In serotyping study using flow-cytometry, bound only to virus with KRIHI. Zolla-Pazner *et al.* [1995] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 257-D: Included a multi-lab study for antibody characterization and assay comparison – best NAb against MN, but not IIIB. D'Souza *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
  - 257-D: Potent MN neutralization, slow dissociation constant. VanCott *et al.* [1994] (**binding affinity**)
  - 257-D: Additive MN or SF2 neutralization when combined with CD4 binding site MAb F105 – does not neutralize RF. Cavacini *et al.* [1993a] (**antibody interactions, variant cross-recognition or cross-neutralization**)
  - 257-D: Neutralizes MN – binds SF2: epitope KSIYI – specificity: MN, SF2, NY5, RF. Gorny *et al.* [1993] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 257-D: Mediated deposition of complement component C3 on HIV infected cells, enhanced by second Ab binding, rabbit anti-human IgG – complement mediated virolysis of MN, but not in the presence of sCD4. Spear *et al.* [1993] (**complement**)
  - 257-D: Reacts with MN, NY5, CDC4 and SF2, does not cross-react with RF, WM52, or HXB2. Karwowska *et al.* [1992b] (**variant cross-recognition or cross-neutralization**)
  - 257-D: Called 257-2-D-IV – potent neutralizing MAb. D'Souza *et al.* [1991]
- No.** 480  
**MAb ID** 311-11-D (311-11D, 311, 311D, 311-D)  
**HXB2 Location** gp160 (305–313)  
**Author Location** gp120 (MN)  
**Epitope** KRIHIGP  
**Subtype** B  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1λ)  
**Ab Type** gp120 V3  
**Research Contact** Susan Zolla-Pazner (Zolla-Pazner@mcrcr6.med.nyu) (NYU Med. Center)  
**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1998; Spear *et al.* 1993; Gorny *et al.* 1993; Gorny *et al.* 1991  
**Keywords** antibody binding site definition and exposure, antibody generation, complement, review, subtype comparisons
- 311-11-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
  - 311-11-D: Called 311: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides do not neutralize as well as V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 311 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
  - 311-11-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most

cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 311-11-D showed weak reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)

- 311-11-D: Review of clade specificity and anti-V3 HIV-1 Abs. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
- 311-11-D: MAb peptide reactivity pattern clustered with immunological related MABs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 311-11-D: Neutralizes MN – binds SF2: KSIYIGP. Gorny *et al.* [1993] (**antibody binding site definition and exposure, antibody generation**)
- 311-11-D: Mediated deposition of complement component C3 on HIV infected cells, enhanced by second Ab binding, rabbit anti-human IgG. Spear *et al.* [1993] (**complement**)

No. 481

**MAb ID** 41148D

**HXB2 Location** gp160 (305–313)

**Author Location** gp120 (MN)

**Epitope** KRIHIGP

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1)

**Ab Type** gp120 V3

**References** Gorny & Zolla-Pazner 2004; Alsmadi & Tilley 1998; Pinter *et al.* 1993b

**Keywords** ADCC, review, variant cross-recognition or cross-neutralization

- 41148D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MABs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. 4117C and 41148D are anti-V3 MABs that neutralize TCLA strains. Gorny & Zolla-Pazner [2004] (**review**)
- 41148D: A study of 6 anti-Env MABs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against strains IIIB, MN, SF-2, comparable to 4117C, however 41148D is 10x less efficient at neutralization, showing ADCC and neutralization don't always correlate. Alsmadi & Tilley [1998] (**ADCC**)
- 41148D: Neutralizes less potently than 4117C, reacts with MN, IIIB, SF2. Pinter *et al.* [1993b] (**variant cross-recognition or cross-neutralization**)

No. 482

**MAb ID** 391/95-D (391-95D, 391.5, 391/95D, 391/95)

**HXB2 Location** gp160 (305–318)

**Author Location** gp120 (MN)

**Epitope** KRIHIGPGRAFV

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

**References** Holl *et al.* 2006a; McCaffrey *et al.* 2004; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; Lawson *et al.* 2002; Guillon *et al.* 2002b; Park *et al.* 2000; Ly & Stamatos 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Stamatos & Cheng-Mayer 1998; Stamatos *et al.* 1997; Seligman *et al.* 1996; Stamatos & Cheng-Mayer 1995; Fontenot *et al.* 1995; Gorny *et al.* 1993; Gorny *et al.* 1991

**Keywords** acute/early infection, antibody binding site definition and exposure, co-receptor, dendritic cells, enhancing activity, neutralization, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 391-D: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 391/95-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MABs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 391/95-D: Called 391/95: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MABs selected using V3 peptides do not show as much ability to neutralize as V3 MABs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 391/95 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 391/95-D: Sera from two HIV+ people and a panel of MABs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of any of the five glycans, within the V3 loop (GM299 V3), C2 (GM292 C2), C3 (GM329 C3), C4 (GM438 C4), or V5 (GM454 V5) made SF162 become sensitive to 391/95-D; SF162 is resistant to 391/95-D neutralization. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure, vaccine antigen design**)
- 391/95-D: The affect of Ab binding on infectivity was studied by pseudotyping three related envs with different phenotypes – R5 viruses were preferentially enhanced, not X4 – the V3 region was the main determinant of Ab-mediated enhancement and modulation of the interaction between CCR5 and gp120 is critical – tests with MABs anti-V3 391/95-D and CD4BS-specific GP68 indicate that Ab specificity did not determine whether or not infectivity was enhanced or neutralized, rather the phenotype was determined by Env conformation. Guillon *et al.* [2002b] (**co-receptor, enhancing activity**)
- 391/95-D: The phenotype and genotype of viral env sequences were studied over a period of seroconversion in one individual – Env trans-complementation demonstrated infectivity

ity of clones derived pre-seroconversion were not influenced by MAb 391/95-D, but post-seroconversion clones were enhanced in the presence of 391/95-D, although the V3 binding region was unchanged – a change in the CD4-binding site was observed (NL43 427 Glu→Lys) to be present in the post-seroconversion 391/95-D enhanced clone (see Guillon *et al.* [2002b]) Lawson *et al.* [2002]. Guillon *et al.* [2002b]; Lawson *et al.* [2002] (**enhancing activity, acute/early infection**)

- 391/95-D: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 391/95-D: Called 391-95D – SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and Ig-GCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000] (**antibody binding site definition and exposure**)
- 391/95-D: Called 391/95D – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000] (**antibody binding site definition and exposure**)
- 391/95-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
- 391/95-D: Called 391.5 – MAb peptide-reactivity pattern clustered with immunological related MAbs: 391.5, 412 and 418, all selected with MN V3 peptide – the core amino acids HIGPGR tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 391/95-D: Called 391-95D – deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V1 or V2 did not enable neutralization by V3 MAbs 391-95D or 257D. Stamatatos &

Cheng-Mayer [1998] (**antibody binding site definition and exposure, subtype comparisons**)

- 391/95-D: Called 391-95D – binds more extensively than MAb 257-D on the surface of HIV-1 isolates SF162 and SF128A – neutralizes more potently than 257-D – stronger neutralization of primary macrophage targets than PBMC – binding post-gp120-sCD4 association related to anti-V3 Abs neutralizing capacity. Stamatatos *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 391/95-D: Competition ELISAs with serial deletions estimated the epitope to be KRIHIGPGRAFY – unconstrained peptide had higher affinity than cyclic. Seligman *et al.* [1996] (**antibody binding site definition and exposure**)
- 391/95-D: The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – V3 loop epitopes were less accessible to Ab binding on the virion surface than in the gp120 monomer, particularly for macrophage-tropic isolates SF162 and SF128a, relative to T-cell tropic SF2 – sCD4 association with gp120 better revealed this V3 epitope on macrophage tropic and dual tropic (MU3) viruses, but not in TCLA SF2. Stamatatos & Cheng-Mayer [1995] (**antibody binding site definition and exposure**)
- 391/95-D: Neutralizes MN – binds to SF2, not IIIB. Gorny *et al.* [1993]

No. 483

MAb ID Aw

HXB2 Location gp160 (305–320)

Author Location gp120 (Gun-1wt)

Epitope KSITIGPGRAFHAI

Neutralizing L

Immunogen vaccine

Vector/Type: peptide Strain: Gun-1 HIV component: V3

Species (Isotype) rat

Ab Type gp120 V3

References McKnight *et al.* 1995

- Aw: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – Aw gives weak neutralization of both wildtype and v strains. McKnight *et al.* [1995]

No. 484

MAb ID Bw

HXB2 Location gp160 (305–320)

Author Location gp120 (Gun-1wt)

Epitope KSITIGPGRAFHAI

Neutralizing L

Immunogen vaccine

Vector/Type: peptide Strain: Gun-1 HIV component: V3

Species (Isotype) rat

Ab Type gp120 V3

References McKnight *et al.* 1995

- Bw: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – Bw gives weak neutralization of only the wildtype strain, does not bind to variant. McKnight *et al.* [1995]

No. 485

**MAb ID** DO142-10 (DO 142-10)

**HXB2 Location** gp160 (305–320)

**Author Location** gp120 (MN)

**Epitope** KRIHIGPGRAFYTT

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1)

**Ab Type** gp120 V3

**References** Gorny & Zolla-Pazner 2004; Kwong *et al.* 2002; Sullivan *et al.* 1998a; Parren *et al.* 1998a; Parren & Burton 1997; Parren *et al.* 1997b; Ditzel *et al.* 1997; Seligman *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, binding affinity, enhancing activity, review, variant cross-recognition or cross-neutralization

- DO124-10: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. DO124-10 neutralizes some TCLA strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- D0124-10: Called D0124. Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- DO142-10: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different that Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs

and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**variant cross-recognition or cross-neutralization, binding affinity**)

- DO124-10: The HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – Fab Ab fragment DO124-10 also enhances YU2 entry, ruling out Fc interactions or Env cross-linking as a mechanism – while DO124-10 enhances YU2 entry 6-fold, it neutralizes HXBc2 under identical conditions. Sullivan *et al.* [1998a] (**enhancing activity, variant cross-recognition or cross-neutralization**)
- DO142-10: Phage expression libraries panned against MN peptide were used to select Fab DO142-10 – Fab binds MN gp120, but not a primary isolate rec gp120. Ditzel *et al.* [1997] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- DO142-10: Neutralizes TCLA strains but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- DO142-10: Binds to gp120 MN and an MN V3 peptide with equal affinity, but binds a consensus B peptide and JRCSF less well, and to IIB gp120 not at all. Parren & Burton [1997] (**variant cross-recognition or cross-neutralization, binding affinity**)
- DO142-10: Fab fragment – competition ELISAs with serial deletions defined the epitope KRIHIGPGRAFYTT. Seligman *et al.* [1996] (**antibody binding site definition and exposure, antibody generation**)

No. 486

**MAb ID** Dv

**HXB2 Location** gp160 (305–320)

**Author Location** gp120 (Gun-1v)

**Epitope** KSITIGSGRAFHAI

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* Gun-1 *HIV component:* V3

**Species (Isotype)** rat

**Ab Type** gp120 V3

**References** McKnight *et al.* 1995

- Dv: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – neutralization of only the variant strain, does not bind to wildtype. McKnight *et al.* [1995]

No. 487

**MAb ID** Fv

**HXB2 Location** gp160 (305–320)

**Author Location** gp120 (Gun-1v)

**Epitope** KSITIGSGRAFHAI

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* Gun-1 *HIV component:* V3

**Species (Isotype)** rat**Ab Type** gp120 V3**References** McKnight *et al.* 1995

- Fv: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – neutralization of only the variant strain, does not bind to wildtype. McKnight *et al.* [1995]

**No.** 488**MAb ID** Gv**HXB2 Location** gp160 (305–320)**Author Location** gp120 (Gun-1v)**Epitope** KSITIGSGRAFHAI**Neutralizing** L**Immunogen** vaccine*Vector/Type:* peptide *Strain:* Gun-1 *HIV component:* V3**Species (Isotype)** rat**Ab Type** gp120 V3**References** McKnight *et al.* 1995

- Gv: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – neutralization of only the variant strain, does not bind to wildtype. McKnight *et al.* [1995]

**No.** 489**MAb ID** Hv**HXB2 Location** gp160 (305–320)**Author Location** gp120 (Gun-1v)**Epitope** KSITIGSGRAFHAI**Neutralizing** L**Immunogen** vaccine*Vector/Type:* peptide *Strain:* Gun-1 *HIV component:* V3**Species (Isotype)** rat**Ab Type** gp120 V3**References** McKnight *et al.* 1995

- Hv: Rat antibodies were raised against V3 peptides that represent either the wildtype (wt), or brain-cell tropic variant (v) of the isolate Gun-1 – neutralization of only the variant strain, does not bind to wildtype. McKnight *et al.* [1995]

**No.** 490**MAb ID** polyclonal**HXB2 Location** gp160 (305–322)**Author Location** gp140 (SF162)**Epitope** KSITIGPGRAFATGD**Neutralizing** yes**Immunogen** vaccine*Vector/Type:* DNA with CMV promotor  
*Strain:* B clade SF162 *HIV component:* gp140 *Adjuvant:* MF59**Species (Isotype)** macaque, rabbit (IgG)**Ab Type** gp120 V3**References** Barnett *et al.* 2001

- SF162ΔV2 is a virus that has a 30 amino acids deletion in the V2 loop that does not abrogate its infectivity but renders it highly susceptible to neutralization – when incorporated into a codon-optimized DNA vaccine with a CMV promoter, delivered by gene gun, SF162Δ2 gave higher neutralizing Ab titers against SF162 than did SF162 itself, and Abs that cross-neutralized non-homologous primary isolates were obtained only when SF162ΔV2, but not intactSF162, was used as the immunogen – NAb titers specific for SF162 increased with multiple immunizations, while titers for non-homologous isolates decreased, but anti-V3 peptide binding Abs were not likely the source of this distinction because anti-V3 titers were much lower than those against the entire envelope, and the second booster immunization did not increase the titer of anti-V3 loop Abs. Barnett *et al.* [2001]

**No.** 491**MAb ID** 50.1 (R/V3-50.1, Fab 50.1)**HXB2 Location** gp160 (306–310)**Author Location** gp120 (MN)**Epitope** RIHIG**Neutralizing** L**Immunogen** vaccine*Vector/Type:* peptide *Strain:* B clade MN  
*HIV component:* V3**Species (Isotype)** mouse (IgG1κ)**Ab Type** gp120 V3**Research Contact** Mary White-Scharf, Repligen Corporation, Cambridge, MA**References** Zhang *et al.* 2002; York *et al.* 2001; Park *et al.* 2000; Hoffman *et al.* 1999; Stanfield *et al.* 1999; LaCasse *et al.* 1998; Berman *et al.* 1997; Seligman *et al.* 1996; Fontenot *et al.* 1995; VanCott *et al.* 1995; Moore *et al.* 1994b; Robert-Guroff *et al.* 1994; VanCott *et al.* 1994; Bou-Habib *et al.* 1994; Rini *et al.* 1993; Ghiara *et al.* 1993; Potts *et al.* 1993; White-Scharf *et al.* 1993; D'Souza *et al.* 1991

- 50.1: NIH AIDS Research and Reference Reagent Program: 1289.
- 50.1: Called R/V3-50.1 – A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- 50.1: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make



- them more susceptible to NAbs alters some step after binding – the dissociation constant,  $K_d$  of 50.1 for the cell associated primary and TCLA Envs was equal, 7nM. York *et al.* [2001]
- 50.1: Called R/V3-50.1 – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MABs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MABs against gp120 by causing conformational changes – 50.1 could only neutralize the sensitive form. Park *et al.* [2000]
  - 50.1: The crystal structure of V3 loop peptides bound to Fabs was obtained – conformational changes in the tip of the V3 loop (GPGR) were observed when different Fabs were bound. Stanfield *et al.* [1999]
  - 50.1: A T-cell line-adapted (TCLA) derivative of SI primary isolate 168P acquired the ability to be neutralized by anti-V3 MABs – the primary isolate could use either CCR5 or CXCR4, and was not neutralized when infection was directed via either pathway, however the TCLA derivative uses CXCR4 only and is neutralized. LaCasse *et al.* [1998]
  - 50.1: Binds to 6/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997]
  - 50.1: Competition ELISAs with serial deletions produced comparable estimate of epitope length to crystal structure and alanine substitution – KRIHIGP. Seligman *et al.* [1996]
  - 50.1: Used to monitor HIV-1 Env expression in infected H9 cells. VanCott *et al.* [1995]
  - 50.1: No neutralization of primary isolate JR-CSF – greater affinity for and neutralization of T cell tropic strain T-CSF, derived from JR-CSF. Bou-Habib *et al.* [1994]
  - 50.1: Shows modest cross-reactivity among B clade gp120s, little outside B clade. Moore *et al.* [1994b]
  - 50.1: Chimeric MN V3 loop in an HXB2 background allows increased FACS signal, Ab affinity, and viral neutralization. Robert-Guroff *et al.* [1994]
  - 50.1: Potent MN neutralization, slow dissociation rate. VanCott *et al.* [1994]
  - 50.1: Crystal structure of a 24 amino acid peptide from the V3 loop bound to 59.1 and 50.1 Fab fragments – epitope KRIHIGP. Ghiara *et al.* [1993]
  - 50.1: No synergistic neutralization of MN when combined with CD4BS MAB F105 – isotype stated to be IgG2a. Potts *et al.* [1993]
  - 50.1: Crystal structure of V3 loop bound to 50.1 – light chain binds just to the left of GPG, heavy chain binds further to the left. Rini *et al.* [1993]
  - 50.1: Epitope defined by peptide reactivity and changes affinity with amino acid substitutions – epitope RIHIGP. White-Scharf *et al.* [1993]
  - 50.1: Called R/V3-50.1 – potent neutralizing of lab strains. D'Souza *et al.* [1991]

No. 492

Mab ID

HXB2 Location gp160 (306–322)

Author Location gp160

Epitope RIRPGRAFVTIGK

Subtype B

Neutralizing

Immunogen vaccine

Vector/Type: influenza Strain: B clade IIIIB  
HIV component: V3

Species (Isotype) human (IgA, IgG)

Ab Type gp120 V3

References Garulli *et al.* 2004

Keywords mucosal immunity

- Progesterone-treated BALB/c mice were intravaginally infected with recombinant influenza A virus (Flu/P18IIIIB), expressing the immunodominant CTL epitope (P18IIIIB, RIRP-GRAFVTIGK, H-2Dd). A second immunization administered 2 weeks after the first doubled serum IgG levels and enabled detection of vaginal IgG. Low levels of vaginal IgA were detected in some animals. Garulli *et al.* [2004] (**mucosal immunity**)

No. 493

Mab ID BAT123 (BAT-123, CGP 47 439)

HXB2 Location gp160 (306–322)

Author Location gp120 (308–322 HXB2)

Epitope RIRIQRGPGRAFVTIGK

Subtype B

Neutralizing L

Immunogen vaccine

Vector/Type: inactivated HIV Strain: B clade IIIIB HIV component: HIV-1

Species (Isotype) mouse (IgG1 $\kappa$ )

Ab Type gp120 V3

Research Contact Tanox Biosystems Inc and David Ho, ADARC, NY

References Gauduin *et al.* 1998; Parren *et al.* 1998a; Andrus *et al.* 1998; Poignard *et al.* 1996a; Sattentau & Moore 1995; Gauduin *et al.* 1995; Pirofski *et al.* 1993; Thali *et al.* 1993; Safrit *et al.* 1993; Moore & Ho 1993; Fung *et al.* 1990; Liou *et al.* 1989; Fung *et al.* 1987

- BAT123: Post-exposure prophylaxis was effective when MAB 694/98-D was delivered 15 min post-exposure to HIV-1 LAI in hu-PBL-SCID mice, but declined to 50% if delivered 60 min post-exposure, and similar time constraints have been observed for HIVIG, 2F5 and 2G12, in contrast to MAB BAT123 that could protect delivered 4 hours post infection. Andrus *et al.* [1998]
- BAT123: Post-exposure passive transfer of murine BAT123 can confer protection to hu-PBL-SCID mice challenged with HIV-1 LAI – this protection is not elicited by CGP 47 439, a BAT123 chimera that has a human IgG1 Fc domain, suggesting that the protection is mediated by complement – the protective ability of BAT123 is lost when mice were treated with cobra venom factor, which inactivates serum complement – IgG1 does not fix complement efficiently so an IgG2 MAB might perform better. Gauduin *et al.* [1998]
- BAT123: The MAB and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]

- BAT123: Epitope described as RGPGRAFVTIGK – V3 MAbs 9284, BAT123, 110.5, and 110.I could each significantly increase gp120 dissociation from virus (BAT123 less so than the others), mimicking sCD4, and expose the gp41 epitope for MAb 50-69, in contrast to anti-V2 MAbs. Poignard *et al.* [1996a]
  - BAT123: Passive transfer of BAT123 to hu-PBL-SCID mice 1 hour prior to inoculation with HIV-1 LAI, or up to four hours post-exposure, could protect mice from infection – the protection, like the MAb, was specific for the viral strain LAI. Gauduin *et al.* [1995]
  - BAT123: Binds with high affinity to monomer and oligomer, rapid association and potent neutralization of lab strain. Sattentau & Moore [1995]
  - BAT123: Called BAT-123 – conformational, does not bind well to denatured gp120 – not reactive with SF-2 gp120 – does not inhibit HIV-1 sera from binding to IIIB gp120. Moore & Ho [1993]
  - BAT123: Variable region sequenced – heavy chain: V 3660-SB32, D unknown, J H3 – light chain: V kappa21, J kappa2. Pirofski *et al.* [1993]
  - BAT123: Passive transfer to Hu-PBS-SCID mice confers protection against challenge with homologous cell-free virus. Safrit *et al.* [1993]
  - BAT123: Anti-idiotypic MAb, AB19-4i, stimulates anti-anti-ID which neutralizes MN and IIIB. Fung *et al.* [1990]
  - BAT123: CGP 47 439 is a BAT123 chimera that has a human IgG1 Fc domain. Liou *et al.* [1989]
- No. 494
- MAb ID** 838-D (838)
- HXB2 Location** gp160 (307–311)
- Author Location** Env (RF)
- Epitope** KSITK
- Subtype** B
- Neutralizing** L
- Immunogen** HIV-1 infection
- Species (Isotype)** human (IgG1 $\lambda$ )
- Ab Type** gp120 V3
- Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)
- References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; He *et al.* 2002; Nyambi *et al.* 2000; Gorny *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Nyambi *et al.* 1998; Hioe *et al.* 1997b; Gorny *et al.* 1997
- Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization
- 838-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
  - 838-D: Called 838: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
  - 838-D: Called 838 – Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS), 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
  - 838-D: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
  - 838-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V3 MAbs 447-52D, 838-D, and 1334 bound with a 7-10 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 838-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 838-D showed intermediate reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
  - 838-D: Review of clade specificity and anti-V3 HIV-1-Abs – this Ab showed strong binding to many A, B, C and F peptides, poor binding to D and E. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
  - 838-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 838, 782, 1027, 908, and 1006, all selected with RF V3 peptide – the core amino acids KSITK tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
  - 838-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – 838-D bound B clade virions but had limited cross-reactivity with other clades, with low levels of binding to A and D virions. Nyambi *et al.* [1998] (**subtype comparisons**)

- 838-D: Five human MAbs against were derived from HIV-infected North American subjects after selection by the V3 RF peptide – 838-D was cross-reactive with V3 peptides from clade A and C, and could bind to 5/8 B clade V3 peptides – 50% neutralization of RF was obtained. Gorny *et al.* [1997] (**antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 838-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

No. 495

**MAb ID** 1006-15D (1006)

**HXB2 Location** gp160 (307–312)

**Author Location** gp120 (RF)

**Epitope** KSITKG

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)

**References** Eda *et al.* 2006b; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; He *et al.* 2002; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1997

**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1006-15D: The neutralization potency of this Ab against 7 HIV-1 primary isolates was compared to the neutralization potency of the Ab KD-247. Same Ab concentrations were needed for neutralization of the N-NIID and 92TH022 isolates, while higher concentrations of 1006-15D were needed for the neutralization of the rest of the HIV-1 isolates suggesting 1006-15D has lower neutralization potency. Eda *et al.* [2006b] (**variant cross-recognition or cross-neutralization**)
- 1006-15D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 1006-15D: Called 1006-15: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and

affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

- 1006-15D: Called 1006 – Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS) , 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- 1006-15D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 1006-15D showed strong cross-reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1006-15D: Review of clade specificity and anti-V3 HIV-1-Abs – this Ab showed strong binding to several B and F peptides, one C peptide, and some reactivity with A peptides – no binding was observed with D and E peptides. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
- 1006-15D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 838, 782, 1027, 908, and 1006, all selected with RF V3 peptide – the core amino acids KSITK tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 1006-15D: Five human MAbs against were derived from HIV-infected North American subjects after selection by the V3 RF peptide – was somewhat cross-reactive with V3 peptides from clade A, C and other B clade V3 peptides, but not E clade. Gorny *et al.* [1997] (**antibody generation, subtype comparisons**)

No. 496

**MAb ID** 782-D (782)

**HXB2 Location** gp160 (307–312)

**Author Location** Env (RF)

**Epitope** KSITKG

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)

**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Hioe *et al.* 1997b; Gorny *et al.* 1997

**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 782-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 782-D: Called 782: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 782-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 782-D showed intermediate reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 782-D: Review of clade specificity and anti-V3 HIV-1-Abs – this Ab showed strong binding to several B and F peptides, one C peptide, and some reactivity with A and D peptides. Zolla-Pazner *et al.* [1999a] (**variant cross-recognition or cross-neutralization, review, subtype comparisons**)
- 782-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 838, 782, 1027, 908, and 1006, all selected with RF V3 peptide – the core amino acids KSITK tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 782-D: Five human MAbs against were derived from HIV-infected North American subjects after selection by the V3 RF peptide – 782-D was not cross-reactive with V3 peptides from clade A or E, but could bind to 3/8 B clade V3 peptides, and 1/2 C clade V3 peptides – 50% neutralization of RF was obtained. Gorny *et al.* [1997] (**antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 782-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

No. 497

MAb ID 908-D (908, 908-12D)

HXB2 Location gp160 (307–312)

Author Location gp120 (RF)

Epitope KSITKG

Subtype B

**Neutralizing L****Immunogen** HIV-1 infection**Species (Isotype)** human (IgG1 $\lambda$ )**Ab Type** gp120 V3**Research Contact** Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1997**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons

- 908-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 908-D: Called 908: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 908-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 908-D showed strong cross-reactivity, but achieved only 50% neutralization on 2/5 isolates tested. Nyambi *et al.* [2000] (**subtype comparisons**)
- 908-D: Review of clade specificity and anti-V3 HIV-1-Abs – this Ab showed strong binding to several A, B, C and F peptides, and poor binding to E and D peptides. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
- 908-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 838, 782, 1027, 908, and 1006, all selected with RF V3 peptide – the core amino acids KSITK tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 908-D: Five human MAbs against were derived from HIV-infected North American subjects after selection by the V3 RF peptide – 908-D was not cross-reactive with V3 peptides from clade E, but could bind to 6/8 B clade V3 peptides, 2/4 A clade, and 1/2 C clade – 50% neutralization of RF was obtained. Gorny *et al.* [1997] (**antibody binding site definition and exposure, antibody generation, subtype comparisons**)

No. 498

MAb ID 1027-15D (1027, 1027-D, 1027D, 1027-15)

HXB2 Location gp160 (307–313)

Author Location Env (RF)

Epitope KSITKGP

Subtype B

Neutralizing no

Immunogen HIV-1 infection

**Species (Isotype)** human (IgG1λ)

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1997

**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons

- 1027-15D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 1027-15S: Called 1027-15: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 1027-15D: Called 1027-D – A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**)
- 1027-15D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 1027-15D showed strong cross-reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1027-15D: Review of clade specificity and anti-V3 HIV-1-Abs – this Ab showed moderate binding to several B and F peptides, one C peptide, and was not reactivity with A, D and E peptides. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
- 1027-15D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 838, 782, 1027, 908, and 1006, all selected with RF V3 peptide – the core amino acids KSITK tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 1027-15D: Five human MAbs against were derived from HIV-infected North American subjects after selection by the V3 RF peptide – 1027-15D was not cross-reactive with V3 peptides from clade A or E, but could bind to 3/8 B clade V3 peptides,

and 1/2 C clade V3 peptides. Gorny *et al.* [1997] (**antibody binding site definition and exposure, antibody generation, subtype comparisons**)

**No.** 499

**MAb ID** F19.26-4

**HXB2 Location** gp160 (307–319)

**Author Location** gp120 (312–324 LAI)

**Epitope** IRIQRGPGRAFVT

**Subtype** B

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG2ak)

**Ab Type** gp120 V3

**References** Boudet *et al.* 1994

- F19.26-4: Strain specific – used to raise anti-idiotypic antibodies. Boudet *et al.* [1994]

**No.** 500

**MAb ID** F19.48-3

**HXB2 Location** gp160 (307–319)

**Author Location** gp120 (312–324 LAI)

**Epitope** IRIQRGPGRAFVT

**Subtype** B

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG2ak)

**Ab Type** gp120 V3

**References** Boudet *et al.* 1994

- F19.48-3: Strain specific – used to raise anti-idiotypic antibodies. Boudet *et al.* [1994]

**No.** 501

**MAb ID** F19.57-11

**HXB2 Location** gp160 (307–319)

**Author Location** gp120 (312–324 LAI)

**Epitope** IRIQRGPGRAFVT

**Subtype** B

**Neutralizing** L (LAI)

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** gp120 V3

**References** Boudet *et al.* 1995; Boudet *et al.* 1994; Boudet *et al.* 1991

- F19.57-11: Anti-anti-idiotypic antibodies (Ab3) were raised in BALBc mice that had greater breadth of reactivity than the original F19.57-11 (Ab3 could also recognize 1282 and SF2, with aa TRK(R or S)IYIGPGRA(WY or FH)T) Boudet *et al.* [1995]
- F19.57-11: MAb F19.57-11 is strain specific for LAI – used to raise anti-idiotypic rabbit antibodies (called 57-B Ab2) Boudet *et al.* [1994]

**No.** 502

**MAb ID** 13105100  
**HXB2 Location** gp160 (307–320)  
**Author Location** gp120 (HXB2)  
**Epitope** IRIQRGPGRAFVTI  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade IIIB  
*HIV component:* V3  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 V3  
**Research Contact** ABI, Columbia, MD  
**References** Dairou *et al.* 2004

**Keywords** antibody binding site definition and exposure

- 13105100: This MAb was raised against the peptide IRIQRGPGRAFVTI, located within the V3 loop flanking the GPGR apical motif. Two MAbs were used to determine the photodamage location in HIV-1 Env induced by sulfonated anionic porphyrins. The negatively charged porphyrins interact with positive charge in the V3 loop. When light activated, they damage amino acid side chains in the C5 region of Env, as evidenced by inhibition of binding of C5 MAb 9201, but not V3 MAb 13105100. Anionic porphyrins could be used in targeted photodynamic decontamination of biological fluids, such as blood, killing HIV without disabling the function of desirable transfusion products. Dairou *et al.* [2004] (**antibody binding site definition and exposure**)

**No.** 503

**MAb ID** M77  
**HXB2 Location** gp160 (307–320)  
**Author Location** gp120 (IIIB)  
**Epitope** IRIQRGPGRAFVTI  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 V3  
**Research Contact** Advanced BioScience Laboratories, Rockville, MD, commercial  
**References** Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Denisova *et al.* 2000; Watkins *et al.* 1996; Denisova *et al.* 1996; Denisova *et al.* 1995; DeVico *et al.* 1995; Cook *et al.* 1994; Watkins *et al.* 1993; di Marzo Veronese *et al.* 1993; di Marzo Veronese *et al.* 1992; Pal *et al.* 1992

**Keywords** antibody binding site definition and exposure, escape, review, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- M77: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. M77 neutralizes some TCLA strains. Gorny & Zolla-Pazner [2004] (**review**)
- M77: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I and Cluster II MAbs required CD4 expression on HIV HXB2 Env expressing HeLa target cells,

but not the CXCR4 co-receptor, binding to a fusion intermediate. Cluster I and II MAbs bound to gp120/gp41 complexes at the cell-to-cell contact interface, in contrast to M77 which bound to gp120 that was evenly dispersed over the target cell surface. Finnegan *et al.* [2002]

- M77: M77 is highly strain specific for IIIB, but anti-idiotypic Abs directed against M77 can in turn elicit an Ab response with expanded HIV cross-reactivity – this mechanism may serve to prolong the primary response and to counter-balance viral immune evasion by mutation. Denisova *et al.* [2000] (**variant cross-recognition or cross-neutralization**)
- M77: Used M77 bound to gp120 as an immunogen – analysis of polyclonal and monoclonal (62 MAbs were generated) response suggests the M77-gp120 immunogen generated MAbs to more linear epitopes than gp120 alone or gp120 bound to CD4. Denisova *et al.* [1996] (**vaccine-specific epitope characteristics**)
- M77: Native M77 is highly strain specific, and V3 binding is primarily dependent on its heavy chain – a light chain switched Fab version of M77 could recognize HIV-1 strains that had substitutions on the left side of the V3 loop – R in GPGR is likely to be critical for binding. Watkins *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
- M77: Reacted with both reduced and non-reduced covalently cross-linked gp120-CD4 complex. DeVico *et al.* [1995] (**antibody binding site definition and exposure**)
- M77: Conformational rearrangements upon binding of M77 to gp120 generates novel epitopes called metatopes. Denisova *et al.* [1995]
- M77: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – this MAb can inhibit gp120 binding to GalCer *in vitro*. Cook *et al.* [1994]
- M77: Stated to be a murine MAb – a neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – M77 neutralization was only slightly reduced by this mutation. Watkins *et al.* [1993] (**escape**)
- M77: Antibody binding to viral isolates from IIIB infected lab worker followed through time – A to T substitution resulted in the loss of neutralization and native gp120 binding, but not peptide binding. di Marzo Veronese *et al.* [1993] (**escape**)
- M77: IIIB-specific MAb, immunoprecipitates deglycosylated form. di Marzo Veronese *et al.* [1992] (**variant cross-recognition or cross-neutralization**)

**No.** 504

**MAb ID** polyclonal  
**HXB2 Location** gp160 (307–321)  
**Author Location** gp120 (307–321)  
**Epitope** IRIQRGPGRAFVTIG  
**Subtype** B  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** chimpanzee  
**Ab Type** gp120 V3  
**References** Goudsmit *et al.* 1988  
**Keywords** antibody binding site definition and exposure, autologous responses, variant cross-recognition or cross-neutralization

- By three months post infection, chimpanzees infected with four strains of HIV-1 developed persistent Ab responses. The V3 loop was a critical binding domain for strain-specific NABs in sera from the infected chimpanzees. Goudsmit *et al.* [1988] (**antibody binding site definition and exposure, autologous responses, variant cross-recognition or cross-neutralization**)

No. 505

**MAB ID** SPBAL114

**HXB2 Location** gp160 (308–317)

**Author Location** gp120 (BAL)

**Epitope** SIHIGPGRAF

**Neutralizing** L

**Immunogen**

**Species (Isotype)** mouse (IgG2ak)

**Ab Type** gp120 V3

**References** Arendrup *et al.* 1995

- Authors suggest that during *in vivo* immunoselection of escape virus, the V3 domain gains increasing resemblance to that of lab strains. Arendrup *et al.* [1995]

No. 506

**MAB ID** SP.SF2:104

**HXB2 Location** gp160 (308–317)

**Author Location** gp120 (SF2)

**Epitope** SIYIGPGRAF

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** (IgG2ak)

**Ab Type** gp120 V3

**References** Arendrup *et al.* 1995; Arendrup *et al.* 1993

- SP.SF2:104: Authors suggest that during *in vivo* immunoselection of escape virus, the V3 domain gains increasing resemblance to lab strains. Arendrup *et al.* [1995]
- SP.SF2:104: Anti-V3 antibody that could neutralize primary virus isolated from a time point of neutralization resistance of autologous virus. Arendrup *et al.* [1993]

No. 507

**MAB ID** polyclonal

**HXB2 Location** gp160 (308–319)

**Author Location** gp120 (304–318 LAI)

**Epitope** RIHIGPGRAFYT

**Subtype** B

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG, IgM)

**Ab Type** gp120 V3

**References** Langedijk *et al.* 1995

- Polyclonal sera from six individuals tested for reactivity against a panel of peptides based on autologous sequences provide evidence for immunological escape mutations in the tip of the V3 loop. Langedijk *et al.* [1995]

No. 508

**MAB ID** 19b

**HXB2 Location** gp160 (308–320)

**Author Location** gp120

**Epitope** -I - - - G - - FY - T

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1)

**Ab Type** gp120 V3

**Research Contact** James Robinson, University of Connecticut, Storrs

**References** Cham *et al.* 2006; Liao *et al.* 2006; Selvarajah *et al.* 2005; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Pognard *et al.* 2003; Kwong *et al.* 2002; Zhang *et al.* 2002; Schulke *et al.* 2002; Kolchinsky *et al.* 2001; Park *et al.* 2000; Binley *et al.* 1999; Trkola *et al.* 1998; Parren *et al.* 1998a; Mondor *et al.* 1998; Parren *et al.* 1997b; Boots *et al.* 1997; Ugolini *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; D'Souza *et al.* 1997; Trkola *et al.* 1996a; Wu *et al.* 1996; Gauduin *et al.* 1996; Sattentau *et al.* 1995; Moore & Ho 1995; Moore *et al.* 1995a; Moore *et al.* 1995b; Sattentau 1995; Moore *et al.* 1994a; Moore *et al.* 1994b; Scott *et al.* 1990

**Keywords** antibody binding site definition and exposure, antibody interactions, neutralization, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 19b: This Ab was shown to infrequently neutralize cloned Envs (clades A, B, C, D, F1, CRF01\_AE, CRF02\_AG, CRF06\_cpx and CRF11\_cpx) derived from donors with and without broadly cross-reactive neutralizing antibodies. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 19b: The gp140 $\delta$ CFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. 19b was shown to bind specifically to all the recombinant proteins as well as to the gp120 from two subtype B isolates. The specific binding of his Ab to CON-S indicated that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure, vaccine antigen design, subtype comparisons**)
- 19b: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V3 MAbs (447-52D, 19b, F245-B4e8 and 39F) bound to the GDMR antigen, but either did not bind or had diminished binding to mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- 19b: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some

- TCLA strains, and a subset also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 19b: This paper attempts to engineer a gp120 molecule that would focus the immune response onto the IgG1b12 epitope. Adding a glycosylation sequon (P313N) to the V3 loop knocked out binding to anti-V3 MAbs loop 2, 19b and 447-52-D. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
  - 19b: Virion capture assays are not a good predictor of neutralization, and the presentation of epitopes using this assay seems to be different from that of functional Envelope spikes on primary isolates – F105 and b6 could efficiently block the b12-mediated capture of infectious virions in a virus capture, but did not inhibit b12 neutralization – while b12 was potent at neutralizing the three primary virions JR-CSF, A DA, and 89.6, the Abs F105, 19b, and Fab b6 were overall very poor neutralizers. Poignard *et al.* [2003]
  - 19b: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
  - 19b: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
  - 19b: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAb 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140. Schulke *et al.* [2002]
  - 19b: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
  - 19b: Mutations in two glycosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYRLINC-NTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, including to 19b. Kolchinsky *et al.* [2001]
  - 19b: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form but 19b was an exception and required around 950 ng/ml to neutralize either form. Park *et al.* [2000]
  - 19b: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAb IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]
  - 19b: Used as a control in this Hx10 binding and neutralizing MAb study because 19b does not bind to Hx10. Mondor *et al.* [1998]
  - 19b: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
  - 19b: No detectable neutralizing activity among primary isolates with different co-receptor usage – some neutralization of TCLA strains. Trkola *et al.* [1998]
  - 19b: Abs that recognize discontinuous epitopes can identify mimotopes from a phage peptide display library – 19b has an epitope involving the tip of the V3 loop, with 5 or 6 essential amino acids distributed within a 12 amino acid stretch – the previously determined binding site was confirmed -I—G—FY—T and some tolerated variants described, the I can be I, V, or



L, the Y can be Y, F, or W – probably a beta-turn is required for FY or FF binding, but WY in can bind with out the context of the turn. Boots *et al.* [1997]

- 19b: In a multilaboratory blinded study, failed to consistently neutralize any of nine B clade primary isolates – there were four sequences with variations in the defined epitope among the 9 isolates tested. D'Souza *et al.* [1997]
- 19b: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 19b bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997]
- 19b: Neutralizes TCLA strains but not primary isolates. Parren *et al.* [1997b]
- 19b: Viral binding inhibition by 19b was weakly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997]
- 19b: Not as effective as IgG1b12 at neutralization *ex vivo* of virus direct from plasma of HIV-1 infected individuals. Gauduin *et al.* [1996]
- 19b: Inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- 19b: MIP-1alpha binding to CCR-5 expressing cells can be inhibited by gp120-sCD4 – binding of 19b blocks this inhibition. Wu *et al.* [1996]
- 19b: Binds to some gp120s from clades A,B,C,E, and F – weakly neutralized some B and one C clade virus. Moore *et al.* [1995b]
- 19b: Despite broad gp120 binding reactivity, not broadly neutralizing. Moore *et al.* [1995a]
- 19b: Review: more broadly cross-reactive than anti-V3 tip MAb 447-D. Moore & Ho [1995]
- 19b: Formalin inactivation of virus at 0.1% formalin for 10 hours at 4 degrees was optimal for inactivation of virus while maintaining epitope integrity. Sattentau *et al.* [1995]
- 19b: V3 loop binding MAb that is more broadly clade cross-reactive than most (binds to 19/29 clade B and 10/12 clade E gp120s) Moore *et al.* [1994b]
- 19b: Competition studies with human sera from seroconverting individuals showed that anti-CD4 BS antibodies can arise very early in infection, comparable or prior to anti-V3 antibodies. Moore *et al.* [1994a]

No. 509

**MAb ID** loop 2 (Loop 2, IgG1 Loop 2, loop2)

**HXB2 Location** gp160 (308–321)

**Author Location** gp120

**Epitope** SISGPGRAFYTG

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 V3

**Research Contact** D. Burton, Scripps Research Institute, La Jolla, CA

**References** Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Sullivan *et al.* 1998a; Parren *et al.* 1998a; Mondor *et al.* 1998; Parren & Burton 1997; Parren *et al.* 1997b; Ugolini *et al.* 1997; Ditzel *et al.* 1997; Wu *et al.* 1996; Moore *et al.* 1994b; Barbas III *et al.* 1993

**Keywords** antibody generation, antibody interactions, antibody sequence variable domain, binding affinity, co-receptor, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- loop 2 database comment: Also known as Loop 2, IgG1 Loop 2 was a obtained by engineering Fab loop2 into an IgG1 molecule. (**antibody generation**)
- loop 2: Called loop2. This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. loop 2 neutralizes some TCLA strains. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- loop 2: This paper attempts to engineer a gp120 molecule that would focus the immune response onto the IgG1b12 epitope. Adding a glycosylation sequon (P313N) to the V3 loop knocked out binding to anti-V3 MAbs loop 2, 19b and 447-52-D. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- loop 2: Called loop2. scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- loop 2: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope – binding affinity of divalent IgG1 loop 2 is only 2-fold greater than monovalent Fab loop 2, suggesting the IgG1 form may bind with only one arm. Parren *et al.* [1998a] (**binding affinity**)
- loop 2: The HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – loop 2 enhances YU2 at concentrations up to 20 ug/ml. Sullivan *et al.* [1998a]
- loop 2: Binds to gp120 from MN and SF2 but not LAI. Ditzel *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- loop 2: Epitope is suggested to be GPGRAF – binds to 10/17 US clade B monomeric gp120s – IgG1 form can neutralize MN and 2 primary isolates tested. Parren & Burton [1997]

- loop 2: Neutralizes TCLA strains but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- loop 2: Viral binding inhibition by loop 2 MAb or Fab was correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997]
- loop 2: MIP-1alpha binding to CCR-5 expressing cells can be inhibited by gp120-sCD4 – binding of loop 2 blocks this inhibition. Wu *et al.* [1996] (**co-receptor**)
- loop 2: Called Loop 2 – shows modest cross-reactivity among B clade gp120s, little outside B clade. Moore *et al.* [1994b] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- loop 2: Sequences of the heavy and light chain Fab variable regions were generated. Barbas III *et al.* [1993] (**antibody sequence variable domain**)

No. 510

Mab ID 4G10

HXB2 Location gp160 (308–322)

Author Location gp120 (308–322 LAI)

Epitope RIQRGPGRAFVTGK

Subtype B

Neutralizing

Immunogen vaccine

Vector/Type: HBcAg fusion HIV component: V3

Species (Isotype) mouse

Ab Type gp120 V3

Research Contact Dr. Albrecht von Brunn, Max-von-Pettenkofer-Institut, Ludwig-Maximilians-Universität München, Germany

References Holl *et al.* 2006a; von Brunn *et al.* 1993

Keywords dendritic cells, neutralization

- 4G10: NIH AIDS Research and Reference Reagent Program: 2534.
- 4G10: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 4G10: A 25 amino acid V3-loop sequence fused to HBcAg enhanced V3 immunogenicity. von Brunn *et al.* [1993]

No. 511

Mab ID 5F7

HXB2 Location gp160 (308–322)

Author Location gp120 (308–322 LAI)

Epitope RIQRGPGRAFVTGK

Subtype B

Neutralizing

Immunogen vaccine

Vector/Type: HBcAg fusion HIV component: V3

Species (Isotype) mouse

Ab Type gp120 V3

Research Contact Dr. Albrecht von Brunn, Max-von-Pettenkofer-Institut, Ludwig-Maximilians-Universität München, Germany

References von Brunn *et al.* 1993

- 5F7: NIH AIDS Research and Reference Reagent Program: 2533.
- 5F7: A 25 amino acid V3-loop sequence fused to HBcAg enhanced V3 immunogenicity. von Brunn *et al.* [1993]

No. 512

Mab ID G3-523

HXB2 Location gp160 (308–322)

Author Location gp120 (308–322)

Epitope RIQRGPGRAFVTIGK

Neutralizing

Immunogen

Species (Isotype) mouse

Ab Type gp120 V3

References Jagodzinski *et al.* 1996; Matsushita *et al.* 1988

- G3-523: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – CRDS inhibits G3-523 binding. Jagodzinski *et al.* [1996]

No. 513

Mab ID MN215

HXB2 Location gp160 (308–322)

Author Location gp120 (MN)

Epitope RIHIGPGRAFYTTKN

Neutralizing L

Immunogen HIV-1 infection

Species (Isotype) human (IgG1)

Ab Type gp120 V3

References Holl *et al.* 2006a; Zipeto *et al.* 2005; Gorny & Zolla-Pazner 2004; Schutten *et al.* 1995b

Keywords antibody binding site definition and exposure, dendritic cells, neutralization, review, vaccine antigen design, variant cross-recognition or cross-neutralization

- MN215: MRC Centralized Facility for AIDS Reagents, NIBSC, UK, EVA3056
- MN215: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- MN215: HIV-1 fusion complexes were prepared from cell lines expressing R5 HIV-1 gp120/gp41 and CD4-CCR5. Neutralizing Abs were raised against both R5 (strain BaL) and X4 (strain 213) viruses. MN215 was used to detect gp120/gp41. Zipeto *et al.* [2005] (**vaccine antigen design**)
- MN215: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. MN215 neutralizes some TCLA strains. Gorny & Zolla-Pazner [2004] (**review**)
- MN215: Minimum epitope for MAB using the Dutch consensus is AFYTTGE, different than defined for MN – generated by EBV transformation of PBMC – displayed higher affinity for NSI than for SI glycoproteins – amino acids HIGP were essential for binding. Schutten *et al.* [1995b] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)

- No. 514  
**MAb ID** Nea 9301  
**HXB2 Location** gp160 (308–323)  
**Author Location** gp120 (IIIB)  
**Epitope** RIQRGPGRAVFTIGKI  
**Neutralizing Immunogen**  
**Species (Isotype)** mouse  
**Ab Type** gp120 V3  
**Research Contact** Dupont, commercial  
**References** Wagner *et al.* 1996
- No. 515  
**MAb ID** 4117C (4117c)  
**HXB2 Location** gp160 (309–315)  
**Author Location** gp120  
**Epitope** IXIGPGR  
**Subtype** B  
**Neutralizing L**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**Ab Type** gp120 V3  
**Research Contact** Abraham Pinter, Public Health Research Institute, Newark, NJ, 07103. pinter@phri.org.  
**References** Pinter *et al.* 2005; Krachmarov *et al.* 2005; Pinter *et al.* 2004; Gorny & Zolla-Pazner 2004; He *et al.* 2002; Alsmadi & Tilley 1998; Pinter *et al.* 1993b; Pinter *et al.* 1993a; di Marzo Veronese *et al.* 1993; Tilley *et al.* 1992; Tilley *et al.* 1991a  
**Keywords** ADCC, antibody binding site definition and exposure, antibody interactions, review, subtype comparisons, variant cross-recognition or cross-neutralization
- 4117c: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from subtype B infected individuals reacted only with subtype B. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Neutralization by anti-V3 B clade specific MAbs 447-52D and 4117C was fully blocked by a clade V3 loop fusion protein, but not an A clade fusion protein, while Cameroonian sera neutralization was fully blocked by both A and B clade fusion proteins. Krachmarov *et al.* [2005] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 4117c: This study is about the MAb C108g, and 4117C was a control. 4117C is a linear V3 epitope unaffected by reduction, whereas C108g, contrary to earlier reports, requires disulfide bonds. C108G is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potentially neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MAbs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Binding to CCR5 was completely inhibited by two V3 MAbs, 4117C and 2219, and was substantially inhibited by

2G12, but was not inhibited by C108g. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)

- 4117c: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. 4117C and 4118D are anti-V3 MAbs that neutralize TCLA strains. Gorny & Zolla-Pazner [2004] (**review**)
- 4117c: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12 which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MAbs, including 4117c, had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigppgrafyTtgE for JR-FL and TigppgrafyAtgD for SF162). Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 4117c: Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS), 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- 4117C: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against MN and SF2, but not IIIB and RF. Alsmadi & Tilley [1998] (**ADCC, variant cross-recognition or cross-neutralization**)
- 4117C: Neutralizes SF2 and MN synergistically combined with anti-CD4 binding site discontinuous Mab. Pinter *et al.* [1993a]; Tilley *et al.* [1992] (**antibody interactions, variant cross-recognition or cross-neutralization**)
- 4117C: Binds V3 loop – does not immunoprecipitate soluble gp120, does react with gp120 on intact virions. Pinter *et al.* [1993b] (**antibody binding site definition and exposure**)
- 4117C: Potent neutralizing activity against MN, SF-2, and NY-5 – synergy with CD4BS MAb 1125H. Tilley *et al.* [1991a] (**antibody binding site definition and exposure, antibody interactions, variant cross-recognition or cross-neutralization**)

No. 516

**MAb ID** 419-D (419, 419D)

**HXB2 Location** gp160 (309–315)

**Author Location** gp120 (MN)

**Epitope** IHIGPGR

**Subtype** B

**Neutralizing L**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zolla-Pazner Center) (NYU Med. Center)

**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; He *et al.* 2002; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Nyambi *et al.* 1998; Hioe *et al.* 1997b; Fontenot *et al.* 1995; Spear *et al.* 1993; Gorny *et al.* 1993; Karwowska *et al.* 1992b

**Keywords** antibody binding site definition and exposure, complement, mimotopes, review, subtype comparisons, superinfection, variant cross-recognition or cross-neutralization

- 419-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 419-D: Called 419: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**mimotopes, superinfection**)
- 419-D: Called 419 – Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS), 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- 419-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 419-D showed intermediate reactivity, and no neutralization when tested against five strains – discrepancy between the epitope as described in earlier papers and as described here, KRIHIGP. Nyambi *et al.* [2000] (**subtype comparisons**)
- 419-D: Review of clade specificity and anti-V3 HIV-1-Abs – epitope is described as KRIHIGP. Zolla-Pazner *et al.* [1999a] (**antibody binding site definition and exposure, review**)
- 419-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 419-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – 419-D bound to 3/4 B clade virions, and to D clade MAL. Nyambi *et al.* [1998] (**subtype comparisons**)
- 419-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of

gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

- 419-D: Neutralizes MN – binds SF2: IYIGPGR. Gorny *et al.* [1993] (**variant cross-recognition or cross-neutralization**)
- 419-D: Mediated deposition of complement component C3 on HIV infected cells, enhanced by second Ab binding, rabbit anti-human IgG. Spear *et al.* [1993] (**complement**)
- 419-D: MN, NY5 and SF2 strain specific, does not cross-react with RF, CDC4, WM52 or HXB2. Karwowska *et al.* [1992b] (**variant cross-recognition or cross-neutralization**)

No. 517

**Mab ID** 453-D (453)

**HXB2 Location** gp160 (309–315)

**Author Location** gp120 (MN)

**Epitope** IHIGPGR

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrc6.med.nyu) (NYU Med. Center)

**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Fontenot *et al.* 1995; VanCott *et al.* 1994; Gorny *et al.* 1993; Gorny *et al.* 1991

**Keywords** antibody binding site definition and exposure, binding affinity, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 453-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**)
- 453-D: Called 453: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 453-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 453-D showed intermediate reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)

- 453-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
- 453-D : MAb peptide-reactivity pattern clustered with immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group – MAb 268, with a previously defined core epitope identical to 453 (HIGPGR), was not part of this reactivity group, illustrating that context can be critical. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 453-D : Called 453, epitope described as KRIHIGPGR – the tip of the V3 loop was presented in a mucin backbone – higher valency correlates with stronger affinity constant. Fontenot *et al.* [1995] (**antibody binding site definition and exposure, vaccine antigen design**)
- 453-D: Moderate homologous neutralization, moderately slow dissociation rate. VanCott *et al.* [1994] (**binding affinity**)
- 453-D: Neutralizes MN – binds SF2: IYIGPGR – specificity: MN, SF2, NY5, RF. Gorny *et al.* [1993] (**antibody binding site definition and exposure**)

No. 518

**MAb ID** 504-D (504, 504-10D)

**HXB2 Location** gp160 (309–315)

**Author Location** gp120 (MN)

**Epitope** IHIGPGR

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mccr6.med.nyu) (NYU Med. Center)

**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1993

**Keywords** antibody binding site definition and exposure, review, subtype comparisons

- 504-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 504-D: Called 504: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 504-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 504-D showed weak reactivity. Nyambi *et al.* [2000] (**subtype comparisons**)

- 504-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review**)
- 504-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)
- 504-D – Neutralizes MN – binds SF2: IYIGPGR. Gorny *et al.* [1993] (**antibody binding site definition and exposure**)

No. 519

**MAb ID** 83.1 (MAb 83.1)

**HXB2 Location** gp160 (309–315)

**Author Location** gp120 (SF2)

**Epitope** IYIGPGR

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade MN

*HIV component:* V3

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 V3

**Research Contact** Mary White-Scharf, Repligen Corporation, Cambridge, MA

**References** Binley *et al.* 1999; Keller & Arora 1999; Jelonek *et al.* 1999; Potts *et al.* 1993; White-Scharf *et al.* 1993

- 83.1: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]
- 83.1: Maternally transferred anti-V3 loop MAb selectively inhibits the anti-V3 loop Ab component of the IgG response to rgp120 SF2 in 21 day old BALBc mice. Jelonek *et al.* [1999]
- 83.1: 19 day old mice injected with 83.1 have a shift in IgG1 response away from the V3 loop upon vaccination, without decreasing the total IgG anti-gp120 response, suggesting that prior treatment with a MAb can mask immunogenic sites and shift the immune response to vaccination. Keller & Arora [1999]
- 83.1: Study of synergism of neutralization and binding comparing F105 and sCD4 with the V3 MAbs: 50.1, 59.1, 83.1, and 58.2 – synergy was observed, and the data suggest that binding of one ligand (F105) can increase the binding of the second (e. g. V3 loop MAbs) due to conformational changes. Potts *et al.* [1993]
- 83.1: Neutralizes SF2. White-Scharf *et al.* [1993]

**No.** 520  
**MAb ID** 5023B  
**HXB2 Location** gp160 (309–316)  
**Author Location** gp120 (309–316 BH10)  
**Epitope** IQRGPGra  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade BH10  
*HIV component:* V3  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 V3  
**References** Langedijk *et al.* 1991  
 • 5023B: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

**No.** 521  
**MAb ID** F58/D1 (F58)  
**HXB2 Location** gp160 (309–316)  
**Author Location** gp120 (IIIB)  
**Epitope** IxxGPGRA  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* virus derived protein *HIV component:* gp120  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 V3  
**References** Heap *et al.* 2005b; Jackson *et al.* 1999; Millar *et al.* 1998; Moore *et al.* 1993b; Levi *et al.* 1993; Broliden *et al.* 1991; Akerblom *et al.* 1990

**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, structure

- F58/D1: Called F58. A 17 amino acid peptide from the CDR-H3 region of F58 retained specificity for gp120 and could neutralize IIIB, although less efficiently than the intact antibody. The F58 MicroAb has a 3-fold faster association rate and a 37.5-fold more rapid dissociation rate than the intact antibody. Such Ab binding site fragments, that retain binding specificity, are called microantibodies. Alanine-substitutions in F58 MicroAb at three positions significantly compromised neutralization but did not reduce binding to soluble gp120, while substitutions at three other positions abrogated both binding and neutralization. The microAb forms a conformationally constrained beta sheet. Heap *et al.* [2005b] (**antibody binding site definition and exposure, antibody sequence variable domain, structure**)
- F58/D1: A 17 amino acid MicroAB was made from the third complementarity-determining region of the heavy chain of MAb – F58 neutralized 5x's more efficiently in terms of mass than the original MAb, 32-fold less on a molar basis – neutralization does not involve initial attachment, but fusion and events in early infection. Jackson *et al.* [1999]
- F58/D1: The interaction of a 17-amino-acid neutralizing microantibody (MicroAB) based on F58 and HIV-1 env was studied by electrospray ionization mass spectrometry. Millar *et al.* [1998]

- F58/D1: Called F58. The complementarity-determining region of F58 was used to create a miniantibody that could neutralize both HIV-1 IIIB and SF2 in vitro. Levi *et al.* [1993] (**antibody binding site definition and exposure, antibody sequence variable domain**)
- F58/D1: Binding to native gp120 1-3 fold greater than to denatured – 314G/W substitution abolishes binding, changes outside the loop have little effect. Moore *et al.* [1993b]

**No.** 522  
**MAb ID** P1/D12  
**HXB2 Location** gp160 (309–316)  
**Author Location** gp120  
**Epitope** IxxGPGRA  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* virus derived protein *Strain:* B clade IIIB *HIV component:* gp120  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 V3  
**References** Moore *et al.* 1993b; Akerblom *et al.* 1990  
 • P1/D12: Binding to native gp120 1-3 fold greater than to denatured – 314G/W substitution abolishes binding, changes outside the loop have little effect. Moore *et al.* [1993b]

**No.** 523  
**MAb ID** P4/D10 (P4D10)  
**HXB2 Location** gp160 (309–316)  
**Author Location** gp120  
**Epitope** IxxGPGRA  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* virus derived protein *Strain:* B clade IIIB *HIV component:* gp120  
**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** gp120 V3  
**References** Schonning *et al.* 1999; Schonning *et al.* 1998; Jacobson 1998; Hinkula *et al.* 1994; Arendrup *et al.* 1993; Moore *et al.* 1993b; Marks *et al.* 1992; Broliden *et al.* 1991; Broliden *et al.* 1990; Akerblom *et al.* 1990  
 • P4/D10: Called P4D10 – the stoichiometry of MAb neutralization was tested and the data indicated that binding for neutralization was incremental not all or none, i.e., each envelope oligomer binds a single MAb and each Env oligomer bound reduces the chances of infection – MAb BC1071 was used for virion quantification – P4D10 binds only to Env with a glycosylation site mutation at the base of the V3 loop A308T. Schonning *et al.* [1999]  
 • P4/D10: Review of passive immunotherapy, summarizing Hinkula *et al.* [1994] in relation to other studies Jacobson [1998]. Hinkula *et al.* [1994]; Jacobson [1998]  
 • P4/D10: Called P4D10 – In a study of the influence of the glycan at position 306 of the V3 loop on MAb recognition, anti-V3 MAbs were found to neutralize an HIV-BRU mutant virus that lacks the V3 loop glycan more efficiently than HIV-BRU – Ab binding site was suggested to be 314-323 of BRU. Schonning *et al.* [1998]

- P4/D10: Used for passive immunotherapy in four late-stage HIV-infected patients – the serum level of p24 did not decrease in any of these four – see also MAb F58/H3. Hinkula *et al.* [1994]
- P4/D10: Primary isolates from different time points from one individual were not susceptible to neutralization by P4/D10. Arendrup *et al.* [1993]
- P4/D10: Binding to native gp120 3 fold greater than to denatured – 314G/W substitution abolishes binding, changes outside the loop have little effect. Moore *et al.* [1993b]
- P4/D10: Variable domain sequenced and is identical to F58/H3. Marks *et al.* [1992]
- P4/D10: Neutralizing and ADCC activity. Broliden *et al.* [1990]

No. 524

MAb ID IIIB-13 V3 (1044-13 IIIB-V3-13 1727)

HXB2 Location gp160 (309–317)

Author Location gp120 (308–316 IIIB)

Epitope IQRGPGRAF

Neutralizing L

Immunogen vaccine

Vector/Type: peptide Strain: B clade IIIB

Species (Isotype) mouse (IgG1)

Ab Type gp120 V3

References Holl *et al.* 2006a; Zhang *et al.* 2002; Chakrabarti *et al.* 2002; Watkins *et al.* 1993; D'Souza *et al.* 1994; Laman *et al.* 1993; Laman *et al.* 1992

Keywords dendritic cells, neutralization

- IIIB-13 V3: Also known as 1044-13 and as IIIB-V3-13 (J. P. Moore, per. comm.)
- IIIB-13 V3: UK Medical Research Council AIDS reagent: ARP3046.
- IIIB-13 V3: NIH AIDS Research and Reference Reagent Program: 1727.
- IIIB-V3 13: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- IIIB-13 V3: Called 1727: Used as a standard for comparing immune responses to modified gp140 (gp140deltaCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation – experiment showed enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002]
- IIIB-13 V3: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]

- IIIB-13 V3: Included in a panel of antibodies used in a multi-lab study for antibody characterization and assay comparison, some neutralization of strains other than IIIB. D'Souza *et al.* [1994]
- IIIB-13 V3: Called IIIB-V3-13 – a neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – IIIB-V3-13 neutralization was only slightly reduced by this mutation. Watkins *et al.* [1993]
- IIIB-13 V3: Neutralizes IIIB but not MN. Laman *et al.* [1992]

No. 525

MAb ID IIIB-34 V3 (IIIB-V3-34)

HXB2 Location gp160 (309–317)

Author Location gp120 (308–316 IIIB)

Epitope IQRGPGRAF

Neutralizing L

Immunogen vaccine

Vector/Type: peptide Strain: B clade IIIB

Species (Isotype) mouse (IgG1)

Ab Type gp120 V3

References Laman *et al.* 1993; Laman *et al.* 1992

- IIIB-34 V3: UK Medical Research Council AIDS reagent: ARP3047.
- IIIB-34 V3: Called IIIB-V3-34 – IIIB strain specific neutralization – binding is reduced somewhat by DTT or SDS-DTT, enhanced by NP40, but binds to native and denatured gp120. Laman *et al.* [1993]
- IIIB-34 V3: Neutralizes IIIB but not MN – QXGPG are critical amino acids for binding by Pepsan analysis. Laman *et al.* [1992]

No. 526

MAb ID A47/B1

HXB2 Location gp160 (309–318)

Author Location gp120 (307–316 IIIB)

Epitope IQRGPGRAV

Neutralizing L

Immunogen vaccine

Vector/Type: protein Strain: B clade IIIB

HIV component: gp120

Species (Isotype) mouse (IgG)

Ab Type gp120 V3

References Akerblom *et al.* 1990

No. 527

MAb ID D59/A2

HXB2 Location gp160 (309–318)

Author Location gp120 (307–316 IIIB)

Epitope IQRGPGRAV

Neutralizing L

Immunogen vaccine

Vector/Type: protein Strain: B clade IIIB

HIV component: gp120

Species (Isotype) mouse (IgG)

Ab Type gp120 V3

References Akerblom *et al.* 1990

No. 528

MAb ID G44/H7

**HXB2 Location** gp160 (309–318)  
**Author Location** gp120 (307–316 IIIB)  
**Epitope** IQRGPGRAFFV  
**Neutralizing** L  
**Immunogen** vaccinia  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 V3  
**References** Akerblom *et al.* 1990

No. 529

**MAb ID** MO96/V3 (M096, M096/V3)  
**HXB2 Location** gp160 (309–318)  
**Author Location** gp120 (309–318)  
**Epitope** IQRGPGRAFFV+AHCNISRAKW  
**Neutralizing**  
**Immunogen** in vitro stimulation or selection  
**Species (Isotype)** human (IgM)  
**Ab Type** gp120 V3  
**References** Gorny & Zolla-Pazner 2004; Ohlin *et al.* 1992  
**Keywords** antibody binding site definition and exposure, antibody generation, review

- M093/V3: Review. provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains; a subset can also neutralize some primary isolates. The three IgMs, M096, M097, and M099, are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- M096/V3: Generated in response to IIIB Env 286-467 upon *in vitro* stimulation of uninfected-donor lymphocytes, and binds to two peptides: 309-318 + 329-338. Ohlin *et al.* [1992] (**antibody binding site definition and exposure, antibody generation**)

No. 530

**MAb ID**  $\mu$ 5.5 (5.5, mu5.5, Rmu5.5)  
**HXB2 Location** gp160 (309–319)  
**Author Location** gp120 (MN)  
**Epitope** IHIGPGRAFFYT  
**Neutralizing** L P  
**Immunogen**  
**Species (Isotype)** mouse (IgG1 $\kappa$ )  
**Ab Type** gp120 V3  
**References** Eda *et al.* 2006b; Okamoto *et al.* 1998; Maeda *et al.* 1992

**Keywords** binding affinity, neutralization, variant cross-recognition or cross-neutralization

- mu5.5: This Ab was shown not to neutralize HIV-1 MNp in spite of the fact that HIV-1 MNp V3 tip sequence is identical to the V3 sequence of this Ab's epitope, suggesting that the neutralization epitope of HIV-1 MNp may be narrower than that of the V3 epitope of R $\mu$ 5.5. R $\mu$ 5.5 also did not neutralize HIV-1 AD8, SHIV 89.6 and SHIV C2/1. The affinity of this Ab was tested for HIV-1 MN. Eda *et al.* [2006b] (**neutralization, variant cross-recognition or cross-neutralization, binding affinity**)

- mu5.5: Rmu5.5 is a humanized antibody of mouse MAb m5.5 – neutralized primary isolates with similar V3 loops – passive transfer of MAb to SCID-hu or hu-PBL-SCID mice conferred protection. Okamoto *et al.* [1998]
- mu5.5: sCD4 causes loss of IIIB type-specificity for MAb 0.5beta, allowing binding and neutralization of MN, in contrast to MAb mu5.5. Maeda *et al.* [1992]

No. 531

**MAb ID**  $\mu$ 5.5 (5.5, mu5.5, Rmu5.5)  
**HXB2 Location** gp160 (309–319)  
**Author Location** gp120 (MN)  
**Epitope** IHIGPGRAFFYT  
**Neutralizing** L P  
**Immunogen**

**Species (Isotype)** mouse (IgG1 $\kappa$ )  
**Ab Type** gp120 V3

**References** Okamoto *et al.* 1998; Maeda *et al.* 1992

- mu5.5: Rmu5.5 is a humanized antibody of mouse MAb m5.5 – neutralized primary isolates with similar V3 loops – passive transfer of MAb to SCID-hu or hu-PBL-SCID mice conferred protection. Okamoto *et al.* [1998]
- mu5.5: sCD4 causes loss of IIIB type-specificity for MAb 0.5beta, allowing binding and neutralization of MN, in contrast to MAb mu5.5. Maeda *et al.* [1992]

No. 532

**MAb ID** 268-D (268-11-D-IV, 268D, 268, 268-11D, 268-10D, MAb 268, 268-10-D, ARP)  
**HXB2 Location** gp160 (310–315)  
**Author Location** gp120 (MN)  
**Epitope** HIGPGR  
**Subtype** B  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mccr6.med.nyu) (NYU Med. Center)

**References** Holl *et al.* 2006a; Lusso *et al.* 2005; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; Vella *et al.* 2002; York *et al.* 2001; Park *et al.* 2000; Nyambi *et al.* 2000; Hioe *et al.* 2000; Laisney & Strosberg 1999; Oggioni *et al.* 1999; Beddows *et al.* 1999; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; LaCasse *et al.* 1998; Stamatatos *et al.* 1997; Hioe *et al.* 1997b; Wisniewski *et al.* 1996; McKeating *et al.* 1996; Fontenot *et al.* 1995; Zolla-Pazner *et al.* 1995; Stamatatos & Cheng-Mayer 1995; VanCott *et al.* 1994; Spear *et al.* 1993; Gorny *et al.* 1993; Karwowska *et al.* 1992b; D'Souza *et al.* 1991; Gorny *et al.* 1991

**Keywords** antibody binding site definition and exposure, dendritic cells, neutralization, review

- 268-D: UK Medical Research Council AIDS reagent: ARP3024.



- 268-D: NIH AIDS Research and Reference Reagent Program: 1511.
- 268-D IV: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 268-D: The epitope for the MAb D19 is conserved and embedded in V3. D19 is unique in that for R5 viruses, it was cryptic and did not bind without exposure to sCD4, and for X4 and R5X4 isolates it was constitutively exposed. It had an overlapping binding region with MAbs 447-52D, B4e8, and 268-D, but different reactivity patterns and fine specificity. Lusso *et al.* [2005]
- 268-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, while many neutralize some TCLA strains, a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 268-D: Called 268: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4 induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides do not show as much ability to neutralize as V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 268 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 268-D: Called ARP3024: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs. Vella *et al.* [2002]
- 268-D: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera—2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5—thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- 268-D: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAb alters some step after binding – one of the TCLA V3 viruses 320SI-C3.3 shows reduced binding with this MAb, the sequence of the epitope in 320SI is HIGPGR and in 320SI-C3.3 is RIGPGR. York *et al.* [2001]
- 268-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – V3 MAbs 447-52-D and 268-10-D did not effect proliferation. Hioe *et al.* [2000]
- 268-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 268-D showed weak reactivity. Nyambi *et al.* [2000]
- 268-D: Called 268D – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
- 268-D: rgp120 derived from a R5X4 subtype B virus, HIV-1 W61D, was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs – 268-D bound rgp120 W61D but could only neutralize the W61D isolate following T-cell line adaptation. Beddows *et al.* [1999]
- 268-D: Called MAb 268 – To identify potential mimotopes of V3, a hexapeptide phage library was screened with MAb 268 – two hexamers were identified, HLGPGR or KAIHRI that bind to 268 with the same binding site as the V3 loop and inhibit 268 MN gp120 – KLH conjugated hexamer KAIHRI stimulates Abs in rabbits that cross-react with ML gp120. Laisney & Strosberg [1999]
- 268-D: Called 268-11D – Study of a live-vector mucosal vaccine that expresses HIV-1 V3 domains using the bacterium *Streptococcus gordonii* which can express heterologous Ag and can colonize the oral cavity and vagina of mice – 268-D and 257-D recognized *S. gordonii* expressing the V3 domain of MN – the vaccine stimulated V3-specific IgG2a in mice. Oggioni *et al.* [1999]
- 268-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a]
- 268-D: Peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group – MAb 453, with an identical core epitope to 268 based on prior experiments (HIGPGR), was not part of this reactivity group, illustrating that context can be critical. Zolla-Pazner *et al.* [1999b]
- 268-D: A T-cell line-adapted (TCLA) derivative of SI primary isolate 168P acquired the ability to be neutralized by anti-V3 MAbs – the primary isolate could use either CCR5 or CXCR4, and was not neutralized when infection was directed via either pathway, however the TCLA derivative uses CXCR4 only and is neutralized. LaCasse *et al.* [1998]
- 268-D: Poor reactivity against HIV-1 isolates SF162 and SF128A and no neutralization, in contrast to MAbs 391/95-D and 257-D. Stamatatos *et al.* [1997]

- 268-D: Failed to neutralize HXB2 and chimeric virus with gp120 from primary isolates in an HXB2 background. McKee *et al.* [1996]
- 268-D: 268-D is V H4 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996]
- 268-D: The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – V3 loop epitopes were less accessible to Ab binding on the virion surface than in the gp120 monomer, particularly for macrophage-tropic isolates SF162 and SF128a, relative to T-cell tropic SF2 – sCD4 association with gp120 did not influence the binding of 268-D to virion-associated gp120, although sCD4 binding did alter epitope exposure for other anti-V3 MAbs. Stamatos & Cheng-Mayer [1995]
- 268-D: Serotyping study using flow-cytometry, if H of HIGPGR was substituted in virus, 268-D did not bind. Zolla-Pazner *et al.* [1995]
- 268-D: Moderate dissociation rate and homologous neutralization titer. VanCott *et al.* [1994]
- 268-D: Neutralizes MN – binds SF2: YIGPGR – specificity: MN, SF2, NY5, RF, CDC4. Gorny *et al.* [1993]
- 268-D: Mediated deposition of complement component C3 on HIV infected cells, but not in the presence of sCD4. Spear *et al.* [1993]
- 268-D: Reacts with MN, NY5, CDC4, RF and SF2, does not cross-react with WM52 or HXB2. Karwowska *et al.* [1992b]
- 268-D: Called 268-11-D-IV – strain specific weakly neutralizing. D'Souza *et al.* [1991]

No. 533

Mab ID 386-D (386, 386-10D, 386D)

HXB2 Location gp160 (310–315)

Author Location gp120 (MN)

Epitope HIGPGR

Subtype B

Neutralizing L

Immunogen HIV-1 infection

Species (Isotype) human (IgG1 $\lambda$ )

Ab Type gp120 V3

Research Contact Susan Zolla-Pazner (Zollas01@mccr6.med.nyu) (NYU Med. Center)

References Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Fontenot *et al.* 1995; VanCott *et al.* 1994; Gorny *et al.* 1993; Karwowska *et al.* 1992b

Keywords antibody binding site definition and exposure, binding affinity, isotype switch, review, subtype comparisons

- 386-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (review)

- 386-D: Called 386: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides do not show as much ability to neutralize as V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 386 was selected using V3 peptides. Gorny *et al.* [2004] (antibody binding site definition and exposure)
- 386-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 386-D showed intermediate reactivity. Nyambi *et al.* [2000] (isotype switch, subtype comparisons)
- 386-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (review, subtype comparisons)
- 386-D: Peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (antibody binding site definition and exposure)
- 386-D: Slow dissociation rate, potent homologous neutralization. VanCott *et al.* [1994] (binding affinity)
- 386-D: Neutralizes MN – binds SF2: YIGPGR – specificity: MN, SF2, NY5, RF, CDC4. Gorny *et al.* [1993] (antibody binding site definition and exposure)

No. 534

Mab ID 5042A

HXB2 Location gp160 (310–315)

Author Location gp120 (310–315 BH10)

Epitope QrGPGR

Neutralizing L

Immunogen vaccine

Vector/Type: peptide Strain: B clade BH10

HIV component: V3

Species (Isotype) mouse (IgG)

Ab Type gp120 V3

References Gorny *et al.* 1991; Langedijk *et al.* 1991

- 5042A: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 535

Mab ID 5042B

HXB2 Location gp160 (310–315)

Author Location gp120 (310–315 BH10)

Epitope QRGPGR

Neutralizing no

Immunogen vaccine

Vector/Type: peptide Strain: B clade BH10

HIV component: V3

Species (Isotype) mouse (IgG)

Ab Type gp120 V3

References Langedijk *et al.* 1991

- 5042B: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 536

Mab ID 418-D (418, 418D)

**HXB2 Location** gp160 (310–316)

**Author Location** gp120 (MN)

**Epitope** HIGPGRA

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mcrchr6.med.nyu) (NYU Med. Center)

**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zhang *et al.* 2002; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Gorny *et al.* 1993; Karwowska *et al.* 1992b

**Keywords** antibody binding site definition and exposure, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 418-D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 418-D: Called 418: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. 418 was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 418-D: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
- 418-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 418-D showed intermediate reactivity. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- 418-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
- 418-D: Called 418 – MAb peptide-reactivity pattern clustered with immunological related MAbs: 391.5, 412 and 418, all selected with MN V3 peptide – the core amino acids HIGPGR tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure**)

- 418-D: Neutralizes MN, does not bind to SF2 or HXB2. Gorny *et al.* [1993] (**variant cross-recognition or cross-neutralization**)
- 418-D: MN strain specific, does not cross-react with SF2, NY5, RF, CDC4 WM52 or HXB2. Karwowska *et al.* [1992b] (**variant cross-recognition or cross-neutralization**)

**No.** 537

**MAb ID** 5021

**HXB2 Location** gp160 (310–316)

**Author Location** gp120

**Epitope** QrGPGRa

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BH10  
*HIV component:* V3

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 V3

**References** Moore *et al.* 1993b; Langedijk *et al.* 1991; Durda *et al.* 1990; Durda *et al.* 1988

- 5021: Binding to native gp120 100-300 fold greater than to denatured – 314G/W substitution abolishes binding, changes outside the loop have little effect. Moore *et al.* [1993b]
- 5021: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

**No.** 538

**MAb ID** 5025B

**HXB2 Location** gp160 (310–316)

**Author Location** gp120 (310–316 BH10)

**Epitope** QRGPGRa

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BH10  
*HIV component:* V3

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 V3

**References** Langedijk *et al.* 1991

- 5025B: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

**No.** 539

**MAb ID** 5042

**HXB2 Location** gp160 (310–316)

**Author Location** gp120

**Epitope** QRGPGRa

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* peptide

**Species (Isotype)** mouse

**Ab Type** gp120 V3

**References** Moore *et al.* 1993b; Durda *et al.* 1990; Durda *et al.* 1988

- 5042: Binding to native gp120 100-300 fold greater than to denatured – 314G/W substitution abolishes binding, changes outside the loop have little effect. Moore *et al.* [1993b]

**No.** 540

**MAb ID** 110.3

**HXB2 Location** gp160 (310–317)

**Author Location** gp120 (308–328 BRU)

**Epitope** QRGPGRAF

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* HIV infected-cell lysate

*Strain:* B clade BRU *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** gp120 V3

**References** Connelly *et al.* 1994; Pirofski *et al.* 1993; Langedijk *et al.* 1992; Evans *et al.* 1989; Thomas *et al.* 1988

- 110.3: An anti-idiotypic MAb generated against 110.3 both mimics and binds to V3, suggesting that the V3 loop may associated with itself. Connelly *et al.* [1994]
- 110.3: MAb variable region sequenced – heavy chain: V 7138(40), D deletion, J H4 – light chain: V kappa21(47), J kappa2. Pirofski *et al.* [1993]
- 110.3: Included as a control. Evans *et al.* [1989]

**No.** 541

**MAb ID** 110.4

**HXB2 Location** gp160 (310–317)

**Author Location** gp120 (308–328 BRU)

**Epitope** QRGPGRAF

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* HIV infected-cell lysate

*Strain:* B clade BRU *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** gp120 V3

**Research Contact** Genetic Systems Corp, Seattle WA, E. Kinney-Thomas

**References** Guillerm *et al.* 1998; Cao *et al.* 1997b; Valenzuela *et al.* 1998; McDougal *et al.* 1996; Connelly *et al.* 1994; Boudet *et al.* 1994; Thali *et al.* 1994; Arendrup *et al.* 1993; Pirofski *et al.* 1993; Thali *et al.* 1993; Langedijk *et al.* 1992; Thali *et al.* 1992b; Callahan *et al.* 1991; Thomas *et al.* 1988

**Keywords** anti-idiotypic, antibody binding site definition and exposure, antibody sequence variable domain, escape

- 110.4: Used for flow cytometry in a study of the anti-CD4, CDR3 loop MAb called 13B8.2, in a study of HIV-1 induced programmed cell death. Guillerm *et al.* [1998]
- 110.4: Neutralization of LAI in CEM cells by anti-V3 MAbs 110.4 and N11-20 is through inhibition of viral binding to the cell. Valenzuela *et al.* [1998]
- 110.4: Virus with the V1-V2 loop deleted was viable and more susceptible to neutralization by CD4i MAb 17b, and anti-V3 MAbs 1121, 9284, and 110.4, but not to and CD4BS MAb F105 or sCD4. Cao *et al.* [1997b] (**antibody binding site definition and exposure**)
- 110.4: Neutralizes HIV-1 LAI. McDougal *et al.* [1996]
- 110.4: An anti-idiotypic MAb generated against 110.3 also blocks binding of 110.4. Connelly *et al.* [1994] (**anti-idiotypic**)

• 110.4: gp41 mutation that confers resistance to neutralization by anti-CD4 binding site antibodies does not reduce neutralizing efficiency of this V3 region MAb. Thali *et al.* [1994] (**antibody binding site definition and exposure**)

• 110.4: Primary isolates from different time points from one individual were not susceptible to neutralization by 110.4. Arendrup *et al.* [1993]

• 110.4: MAb variable region sequenced – heavy chain: V 3660-SB32, D closest to DSP2.3, 2.4 and .6, J H2 – light chain: V kappa21, J kappa2. Pirofski *et al.* [1993] (**antibody sequence variable domain**)

• 110.4: 313 P/S substitution in the V3 region disrupts binding. Thali *et al.* [1992b] (**antibody binding site definition and exposure, escape**)

• 110.4: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interactions mediated through the local high positive charge density in the V3 loop. The binding of this anti-V3 antibody is inhibited by dextran sulfate. Callahan *et al.* [1991]

**No.** 542

**MAb ID** 110.5

**HXB2 Location** gp160 (310–317)

**Author Location** gp120 (308–328 BRU)

**Epitope** QRGPGRAF

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* HIV infected-cell lysate

*Strain:* B clade BRU *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** gp120 V3

**Research Contact** E. Kinney-Thomas or Genetic Systems, Seattle WA

**References** Parren *et al.* 1998a; Ugolini *et al.* 1997; Binley *et al.* 1997a; Jeffs *et al.* 1996; McDougal *et al.* 1996; Pognard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Sattentau *et al.* 1995; Klasse *et al.* 1993a; Thali *et al.* 1993; Moore *et al.* 1993b; Pirofski *et al.* 1993; McKeating *et al.* 1992a; Langedijk *et al.* 1992; Sattentau & Moore 1991; Cordell *et al.* 1991; Moore *et al.* 1990; Thomas *et al.* 1988; Reitz *et al.* 1988

• 110.5: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]

• 110.5: Viral binding inhibition by 110.5 was correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997]

• 110.5: Deletion of the V1V2 regions did not affect anti-V3 Abs ability to bind when compared to intact rec gp120. Jeffs *et al.* [1996]

• 110.5: Neutralizes HIV-1 LAI. McDougal *et al.* [1996]

• 110.5: Reciprocal binding inhibition with other anti-V3 MAbs – enhances binding of some anti-V2 MAbs – binding enhanced by some CD4 binding site MAbs. Moore & Sodroski [1996]

- 110.5: Did not induce dissociation of gp120, as sCD4 did – discrepancy with Poignard *et al.* [1996a], that was suggested to be due to MAb interference with detection, as the gp120-MAB complex was denatured in the Poignard study Moore *et al.* [1990]. Moore *et al.* [1990]; Poignard *et al.* [1996a]
- 110.5: V3 MAbs 9284, BAT123, 110.5, and 110.I could each significantly increase gp120 dissociation from virus, mimicking sCD4, and expose the gp41 epitope for MAb 50-69, in contrast to anti-V2 MAbs. Poignard *et al.* [1996a]
- 110.5: Pretreatment of HX10-infected H9 cells with sCD4 decreases signal from 110.5 at 37 degrees due to dissociation of gp120-gp41. Sattentau *et al.* [1995]
- 110.5: Binds with high affinity to monomer and oligomer, rapid association and potent neutralization of lab strains – neutralizes cell-free Hx10. Sattentau & Moore [1995]
- 110.5: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to conformationally sensitive neutralizing MAbs – neutralization efficiency of 110.5 is not affected. Klasse *et al.* [1993a]; Reitz *et al.* [1988]
- 110.5: Thrombin cleavage of V3 loop between R-315 and A-316 abrogates binding – can inhibit C4 region antibody which has conformational requirements (G3-299) – binding to native gp120 100-300 fold greater than to denatured. Moore *et al.* [1993b]
- 110.5: Variable region sequenced – heavy chain: V 3660-SB32, D closest to DSP2.3, 2.4 and .6, J H2 – light chain: V kappa21, J kappa2. Pirofski *et al.* [1993]
- 110.5: Binding insensitive to gp120 reduction. Cordell *et al.* [1991]
- 110.5: Two fold increase in binding to gp120 in the presence of bound sCD4. Sattentau & Moore [1991]

No. 543

MAb ID 58.2

HXB2 Location gp160 (310–317)

Author Location gp120 (MN)

Epitope HIGPGRAF

Neutralizing L

Immunogen vaccine

Vector/Type: peptide Strain: B clade MN  
HIV component: V3

Species (Isotype) mouse (IgG1κ)

Ab Type gp120 V3

Research Contact Repligen Corp.

References Binley *et al.* 2004; York *et al.* 2001; Stanfield *et al.* 1999; Seligman *et al.* 1996; Moore *et al.* 1994b; Potts *et al.* 1993; White-Scharf *et al.* 1993

Keywords subtype comparisons, variant cross-recognition or cross-neutralization

- 58.2: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. 58.2 could only neutralize B subtype viruses, and seemed to have a minimal epitope of (H/T)IGPGR(A/T)(F/L). Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

- 58.2: 58.2's epitope was noted to be IGPGRAF – Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NABs alters some step after binding. York *et al.* [2001]
- 58.2: The crystal structure of Fab 58.2 bound to V3 loop peptides was obtained – conformational changes in the tip of the V3 loop (GPGR) were observed when different MAbs were bound – 58.2's epitope was defined as KRKRIHIGPGRFY. Stanfield *et al.* [1999]
- 58.2: Competition ELISAs with serial deletions produced longer estimates of epitope length, RIHIGPGRFY, than Alanine substitution, suggesting significance of non-contact residues. Seligman *et al.* [1996]
- 58.2: Modest cross-reactivity among B clade gp120s, little outside B clade – core epitope as I-IHIG. Moore *et al.* [1994b]
- 58.2: Did not synergistically neutralize MN in combination with MAb F105 – there was synergistic neutralization when combined with sCD4. Potts *et al.* [1993]
- 58.2: Epitope defined by peptide reactivity and changes in affinity with amino acid substitutions – 4/7 primarily isolates were neutralized. White-Scharf *et al.* [1993]

No. 544

MAb ID polyclonal

HXB2 Location gp160 (310–318)

Author Location gp120

Epitope QRGPGRAFV?

Neutralizing L

Immunogen vaccine

Vector/Type: peptide keyhole limpet hemo-cyanin (KLH) conjugate, peptide Brucella abortus (Ba) conjugate, peptide lipopolysaccharide (LPS) conjugate Strain: B clade MN HIV component: V3

Species (Isotype) mouse (IgA, IgG1, IgG2a)

References Golding *et al.* 2002a

- Intranasal (i.n.) immunization with V3-Ba induced mucosal anti-V3 NABs and IFN-gamma secreting T cells – V3-Ba, V3-KLH and V3-LPS could each induce serum and mucosal IgA and IgG in BALB/c mice – i.n. plus i.p. immunizations gave higher titers than i.n. alone – the response to V3-KLH was mainly restricted to IgG1, and to V3-Ba, IgG2a – class II KO mice (CD4+ deficient) did not respond to V3-KLH, but did respond to V3-Ba, suggesting that V3-Ba may be effective in eliciting Ab responses in HIV-1 infected individuals that have impaired CD4+ T cell function. Golding *et al.* [2002a]

No. 545

MAb ID KD-247

HXB2 Location gp160 (311–315)

Author Location (MOKW)

Epitope IGPGR

Subtype B

Neutralizing P

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade, B clade MN, B clade RF, Other *HIV component:* V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** humanized mouse (IgG)

**Ab Type** gp120 V3

**Research Contact** Shuzo Matsushita, Kumamoto University, Japan shuzo@kaiju.medic.kumamoto-u.ac.jp

**References** Shibata *et al.* 2007; Eda *et al.* 2006b; Eda *et al.* 2006a

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, binding affinity, escape, immunoprophylaxis, variant cross-recognition or cross-neutralization

- KD-247: Escape variants were induced by exposing the HIV-1 strain MOKW to different concentrations of KD-247 in vitro. In the presence of relatively low concentrations of the Ab, viral variants with V2 mutations R166K and D167N were found with partial resistance against KD-247. In the presence of high concentrations of KD-247, in addition to the V2 mutations, a V3 tip mutation (P313L) expanded inducing complete resistance to KD-247. V2 P175L substitution conferred high resistance to KD-247, however, additional KN substitutions in positions 166 and 167 resulted in a less resistant virus with a replication advantage. Shibata *et al.* [2007] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, escape, binding affinity**)
- KD-247: A new humanize MAb recognizing the V3 tip sequence was generated by transferring the genes of the complementary determining region of the mouse NAb C25 into genes of a human V region. C25 was raised by serial vaccinations of a mouse with distinctive six B clade V3 loop peptides. KD-247 was shown to neutralize laboratory and primary isolates of CXCR4 and CCR5 viruses that possess a GPGR sequence in the Env V3 tip region more effectively than any of the reference Abs used in the study. KD-247 was shown to recognize the narrow V3 tip sequence with high affinity. Eda *et al.* [2006b] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, binding affinity, antibody sequence variable domain**)
- KD-247: This Ab was shown to efficiently neutralize clade B and B' CXCR4 and CCR5 HIV-1 primary isolates with matching V3 sequence motifs while it did not neutralize sequence-mismatched clade B and E isolates. It was also shown to provide sterile protection against SHIV challenge when passively transferred to monkeys in a single high dose. Lower doses provided partial protection. Eda *et al.* [2006a] (**immunoprophylaxis, variant cross-recognition or cross-neutralization**)

**No.** 546

**MAb ID** 537-D (537)

**HXB2 Location** gp160 (311–315)

**Author Location** gp120 (MN)

**Epitope** IGPGR

**Subtype** B

**Neutralizing L**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)

**References** Gorny *et al.* 2004; Nyambi *et al.* 2000; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Fontenot *et al.* 1995; VanCott *et al.* 1994; Gorny *et al.* 1993; Gorny *et al.* 1992; Karwowska *et al.* 1992b

**Keywords** antibody binding site definition and exposure

- 537-D: Called 537: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 537-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 537-D showed weak reactivity. Nyambi *et al.* [2000]
- 537-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a]
- 537-D: MAb peptide-reactivity pattern clustered with immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b]
- 537-D: Moderate homologous neutralization, relatively rapid dissociation constant. VanCott *et al.* [1994]
- 537-D: MN type specific neutralization observed – binds SF2, also IGPGR. Gorny *et al.* [1992, 1993]
- 537-D: Reacts with MN, NY5, CDC4, RF, WM52 and SF2, but does not cross-react with HXB2. Karwowska *et al.* [1992b]

**No.** 547

**MAb ID** 5020

**HXB2 Location** gp160 (311–316)

**Author Location** gp120 (311–316 BH10)

**Epitope** RGPGR

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BH10  
*HIV component:* V3

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 V3

**References** Langedijk *et al.* 1991

- 5020: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

**No.** 548

**MAb ID** RC25

**HXB2 Location** gp160 (311–316)

**Author Location** gp120 (JRFL)

**Epitope** IGPGRA

**Subtype** B

**Neutralizing** L

**Immunogen**

**Species (Isotype)** humanized mouse

**Ab Type** gp120 V3

**References** Kaizu *et al.* 2003; Kimura *et al.* 2002

**Keywords** co-receptor, HAART, ART

- RC25: MD14 is a R5X4 SHIV with a B clade Env; the V3 loop of an E-clade Env was inserted into MD14 to create SHIV-TH09V3, an R5 virus. SHIV-TH09V3 could infect both cynomolgous and pig-tailed macaques, and the R5 co-receptor usage was maintained after passage through macaques. The MAb RC25 recognized B clade V3 loops, and reacted with SHIV-MD14. Rabbit anti-sera raised against a NSI Clade E consensus preferentially recognized SHIV-TH09V3. Kaizu *et al.* [2003] (**co-receptor**)
- RC25: RC25 is a humanized MAb that recognizes the epitope IGPGRA – it has strong neutralizing activity against JRFL (R5 virus) and weak against NL4-3 (X4 virus) and is used as a control in a study of NAb activity in patients undergoing HAART. Kimura *et al.* [2002] (**HAART, ART**)

**No.** 549

**MAb ID** 5023A (5023, NEA-9205, NEA 9205)

**HXB2 Location** gp160 (311–317)

**Author Location** gp120 (311–317 BH10)

**Epitope** RgPGRAF

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade BH10  
*HIV component:* V3

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 V3

**Research Contact** Paul Durda, Du Pont de Nemours and Co

**References** Schonning *et al.* 1998; Rovinski *et al.* 1995; Back *et al.* 1993; D'Souza *et al.* 1991; Langedijk *et al.* 1991

- 5023A: Called NEA-9205 – The N306 glycan of the V3 loop makes the tip of the V3 loop inaccessible to this MAb in oligomeric Env, loss of this glycan enhances neutralization sensitivity. Schonning *et al.* [1998]
- 5023A: Called 5023 in this paper – Used to precipitate gp160 in immunoblots in a study examining the feasibility of using unprocessed gp160 glycoprotein as an immunogen. Rovinski *et al.* [1995]
- 5023A: Called 5023 – Langedijk also has an MAb called 5023B – gp41 amino acid substitutions 668 (N/S) and 675 (I/M) in gp41 interfere with 5023s neutralization potency, region 662-675 is ELDKWANLWNWFNI. Back *et al.* [1993]
- 5023A: Called 5023 – Langedijk also has an MAb called 5023B – strong cross-reactive neutralizing MAb. D'Souza *et al.* [1991]
- 5023A: Generation and Fine mapping of murine MAbs. Langedijk *et al.* [1991]

**No.** 550

**MAb ID** 110.6

**HXB2 Location** gp160 (311–318)

**Author Location** gp120 (BRU)

**Epitope** RGPGRAFV

**Neutralizing** L (weak)

**Immunogen** vaccine

*Vector/Type:* HIV infected-cell lysate

*Strain:* B clade BRU *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1 $\lambda$ )

**Ab Type** gp120 V3

**References** Langedijk *et al.* 1992; Pirofski *et al.* 1993; Thomas *et al.* 1988

- 110.6: Variable region sequenced – heavy chain: V J558-146b.1alpha, D closest to DSP16.2, J H3 – light chain: V lambda1, J lambda1. Pirofski *et al.* [1993]

**No.** 551

**MAb ID** polyclonal

**HXB2 Location** gp160 (311–318)

**Author Location** gp120 (MN)

**Epitope** IGPGRAFV

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* B. abortus complex *Strain:* B clade MN, B clade SF2 *HIV component:* gp120

**Species (Isotype)** mouse (IgG2a)

**Ab Type** gp120 V3

**References** Golding *et al.* 1995

- Ab is evoked even in mice depleted of CD4+ cells. Golding *et al.* [1995]

**No.** 552

**MAb ID** 10/36e

**HXB2 Location** gp160 (311–321)

**Author Location** gp120 (311–321 HXB10)

**Epitope** RGPGRAFVTIG

**Neutralizing** L (HXB10)

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120

**Species (Isotype)** rat (IgG2a)

**Ab Type** gp120 V3

**References** Peet *et al.* 1998; McKeating *et al.* 1993b; McKeating *et al.* 1992a

- 10/36e: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, but anti-V3 MAb 10/36e binding was dramatically diminished by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 10/36e: Binding to virion gp120 enhanced by sCD4. McKeating *et al.* [1992a]

**No.** 553

**MAb ID** 10/54 (10/54ow/6i/6i)

**HXB2 Location** gp160 (311–321)

**Author Location** gp120 (311–321 HXB10)

**Epitope** RGPGRAFVTIG

**Neutralizing** L (HXB10)  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120

**Species (Isotype)** rat (IgG1)

**Ab Type** gp120 V3

**References** Peet *et al.* 1998; McKeating *et al.* 1993b; McKeating *et al.* 1993a; McKeating *et al.* 1992a

- 10/54: Called 10/54ow/6i/6i: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MABs to V1/V2, C1 and C4 to bind, but anti-V3 MAB 10/54 binding was dramatically diminished by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wild-type, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- 10/54: Studied in the context of a neutralization escape mutant. McKeating *et al.* [1993a]
- 10/54: Binding to virion gp120 enhanced by sCD4. McKeating *et al.* [1992a]

**No.** 554

**MAB ID** 11/85b (11/85b/14I/14I)

**HXB2 Location** gp160 (311–321)

**Author Location** gp120 (311–321 HXB10)

**Epitope** RGPGRFVTIG

**Neutralizing** L (HXB2)

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120

**Species (Isotype)** rat (IgG2b)

**Ab Type** gp120 V3

**References** McKeating *et al.* 1993b; McKeating *et al.* 1992a

- 11/85b: Binding to virion gp120 enhanced by sCD4. McKeating *et al.* [1992a]

**No.** 555

**MAB ID** polyclonal

**HXB2 Location** gp160 (311–322)

**Author Location** gp120 (MN)

**Epitope** IGPGRFYTTKN

**Neutralizing** L (MN ALA-1)

**Immunogen** vaccine

*Vector/Type:* human rhinovirus 14 *Strain:* B clade MN *HIV component:* V3

**Species (Isotype)** guinea pig

**Ab Type** gp120 V3

**References** Smith *et al.* 1998

- The tip of the MN V3 loop (IGPGRFYTTKN) was inserted into cold-causing human rhinovirus 14 (HRV14) – chimeras were immunoselected, and chimeric viruses were neutralized by anti-V3 loop antibodies – chimeric viruses elicited potent NABs against ALA-1 and MN. Smith *et al.* [1998]

**No.** 556

**MAB ID** 0.5β (0.5 beta, 0.5beta)

**HXB2 Location** gp160 (311–324)

**Author Location** gp120 (316–330 HXB2)

**Epitope** RGPGRFVTIGKIG

**Subtype** B

**Neutralizing** L (IIIB)

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* Env

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** gp120 V3

**Research Contact** Shuzo Matsushita or Toshio Hattori of Kumamoto University

**References** Garcia *et al.* 2006; Harada *et al.* 2004; Kawai *et al.* 2003; Zvi *et al.* 2000; Tugarinov *et al.* 2000; Jagodzinski & Trzeciak 2000; Fortin *et al.* 2000; Tugarinov *et al.* 1999; Faiman & Horovitz 1997; Wyatt *et al.* 1997; Zvi *et al.* 1997; Huang *et al.* 1997; Faiman *et al.* 1996; Jeffs *et al.* 1996; McDougal *et al.* 1996; Warrior *et al.* 1996; Jagodzinski *et al.* 1996; Zvi *et al.* 1995a; Zvi *et al.* 1995b; Broder *et al.* 1994; Boudet *et al.* 1994; Okada *et al.* 1994; Thali *et al.* 1994; Cook *et al.* 1994; Watkins *et al.* 1993; Klasse *et al.* 1993a; Moore *et al.* 1993b; di Marzo Veronese *et al.* 1993; Sperlagh *et al.* 1993; McKeating *et al.* 1992a; Maeda *et al.* 1992; Emimi *et al.* 1992; Matsushita *et al.* 1992; D'Souza *et al.* 1991; Nara *et al.* 1990; Reitz *et al.* 1988; Skinner *et al.* 1988a; Skinner *et al.* 1988b; Matsushita *et al.* 1988

**Keywords** anti-idiotypic, antibody binding site definition and exposure, antibody generation, antibody interactions, binding affinity, brain/CSF, co-receptor, complement, escape, mimics, structure, variant cross-recognition or cross-neutralization

- 0.5beta: UK Medical Research Council AIDS reagent: ARP3025.
- 0.5beta: NIH AIDS Research and Reference Reagent Program: 1591.
- 0.5beta: The affinity of this Ab was measured for three peptides, one representing the sequence of the V3 loop of HIV-1 IIIB strain and the other two having thiazolidine derivatives replacing the proline within the GPGR. None of the replacements had a large effect on binding of the Ab but the replacement with 2,2 dimethylthiazolidine behaved more like the wildtype. This and the structural and conformational studies by NMR and modeling indicate that it can successfully be used to mimic the native peptide. Garcia *et al.* [2006] (**antibody binding site definition and exposure, mimics, binding affinity, structure**)
- 0.5beta: Studies on the temperature dependence of infectious virus (increased temperatures up to 37 degrees increases infectivity) showed that X4 pseudoviruses that were infectious at room temperature were also more resistant to anti-V3 0.5beta and anti-CXCR4 blocking peptide T140. This implies that virus more heavily populated with functional envelopes are more infectious. Harada *et al.* [2004] (**co-receptor**)



- 0.5beta: 0.5beta was used as a control for gp120 expression relative to Nef expression soon after infection of cultures. The goal of this study was to elicit anti-Nef IgM human Abs in trans-chromosome mice that carry human chromosomes responsible for Ig production. These mice were immunized with recombinant Nef protein. Human heavy chain, mouse light chain anti-Nef IgM were obtained. The hope was that these human IgM anti-Nef chimeric Abs would activate complement mediated cytolysis; C3 deposition was induced but not at high enough levels to induce lysis. Kawai *et al.* [2003] (**complement**)
- 0.5beta: Host encoded intercellular adhesion molecule (ICAM-1) is incorporated by the HIV-1 virion and enhances viral infectivity – ICAM-1 does not modify virus sensitivity to antibodies 0.5beta or 4.8D or sCD4, but neutralizing ability of F105 was diminished in ICAM bearing virions in the presence of lymphocyte function-association antigen-1 (LFA-1) Ab. Fortin *et al.* [2000] (**antibody interactions**)
- 0.5beta: MAbs 0.5beta and G3-42 were used to study synthesis of oligomeric and monomeric forms of Env – inhibition of glycosylation by tunicamycin results in reduction of oligomeric gp120 at the cell surface and of monomer in the cytoplasm – neither MAb recognized non-glycosylated Env precursor. Jagodzinski & Trzeciak [2000]
- 0.5beta: 14/18 residues of peptide P1053, RKSIRIQRGP-GRFVTIG, were shown to be involved in the Ab recognition site using NMR – QRGPGR forms a beta-hairpin turn at the center of the binding pocket. Tugarinov *et al.* [2000] (**antibody binding site definition and exposure**)
- 0.5beta: NMR and mutation cycles were employed to generate a model of the peptide-antibody complex, showing aa residues that interact or do not contribute to the binding of MAb 0.5beta Fv with the peptide – F96(L) of 0.5beta binds to Pro13, H52(H) interacts with Ile7, Ile9, Gln10, and D56(H) interacts with Arg11 of the V3 loop peptide – RGPG retains hairpin conformation binds in the center of a groove. Zvi *et al.* [2000] (**structure**)
- 0.5beta: NMR structure reveals that Ab bound IIIB-V3 peptide adopts an unexpected type VI cis proline beta-turn. Tugarinov *et al.* [1999] (**structure**)
- 0.5beta: The Fv fragment was purified and the temperature dependence and effect of mutations was studied. Faiman & Horovitz [1997]
- 0.5beta: Relative to the native peptide, an O-linked alpha-galactosamine modified V3 peptide enhanced binding to 0.5beta, while an N-linked beta-glucosamine modified peptide showed reduced binding. Huang *et al.* [1997] (**antibody binding site definition and exposure**)
- 0.5beta: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- 0.5beta: The structure of a 17 amino acid V3 peptide bound to the Fab was studied using NMR. Zvi *et al.* [1997] (**structure**)
- 0.5beta: For Fv fragment of 0.5beta, the combined variable regions of the heavy and light chain residues, were purified. Binding of the V3 peptide epitope TRKSIRIQRGP-GRFVTIGK was studied through mutagenesis of arginines and the free energy of binding in various salt concentrations. R4A, R8A, and R11A all reduce the free energy; R8 is embedded in the peptide-Fv fragment, while R11 is more solvent exposed. Faiman *et al.* [1996] (**antibody binding site definition and exposure**)
- 0.5beta: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – CRDS inhibits 0.5beta binding – 0.5beta epitope described as GPGRFVTIG. Jagodzinski *et al.* [1996]
- 0.5beta: Deletion of the V1V2 regions did not affect anti-V3 Abs ability to bind when compared to intact rec gp120. Jeffs *et al.* [1996] (**antibody binding site definition and exposure**)
- 0.5beta: Synergistic neutralization of HIV-1 when combined with anti-V2 MAb C108G. Warrier *et al.* [1996] (**antibody interactions**)
- 0.5beta: The interactions of the peptide RKSIRIQRGP-GRFVT 0.5beta were studied by NMR, and hydrophobic interactions between the two Is and the V form the base of a 12 amino acid loop with GPGR at the apex. Zvi *et al.* [1995b] (**antibody binding site definition and exposure**)
- 0.5beta: NMR of 0.5beta bound NNTRKSIRIQRGP-GRFVTIGKIG suggests that the bound amino acids are in the region SIRIQRGPGRFVT. Zvi *et al.* [1995a] (**antibody binding site definition and exposure**)
- 0.5beta: Type-specific neutralization of IIIB – does not neutralize SF2. Broder *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 0.5beta: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – this MAb can inhibit gp120 binding to GalCer *in vitro*. Cook *et al.* [1994] (**brain/CSF**)
- 0.5beta: Binding domain aa 310-319: RGPGRFVTIGKIG – mutations in the V3 loop from basic residues can destroy virus infectivity and syncytium formation: R306T, R309T and R313G can also reduce binding of V3 MAbs with two different binding sites: 9284 and 0.5beta. Okada *et al.* [1994] (**antibody binding site definition and exposure**)
- 0.5beta: gp41 mutation that confers resistance to neutralization by anti-CD4 binding site antibodies does not reduce neutralizing efficiency of this V3 region MAb. Thali *et al.* [1994]
- 0.5beta: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to some antiserum and conformationally sensitive neutralizing MAbs – neutralization efficiency of 0.5beta is not affected. Klasse *et al.* [1993a]; Reitz *et al.* [1988] (**antibody binding site definition and exposure**)
- 0.5beta: Binding to native gp120 100-300 fold greater than to denatured. Moore *et al.* [1993b] (**antibody binding site definition and exposure**)
- 0.5beta: Monoclonal anti-idiotypic antibodies that mimic the 0.5beta epitope were generated. Sperlagh *et al.* [1993] (**anti-idiotypic**)
- 0.5beta: A neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – of the MAbs tested, 0.5beta neutralization was the most profoundly affected by this mutation. Watkins *et al.* [1993] (**escape**)
- 0.5beta: Neutralization of virus carrying an A to T substitution (contrast with MAb M77) di Marzo Veronese *et al.* [1993]

- 0.5beta: sCD4 causes loss of IIIB type-specificity, allowing binding and neutralization of MN, in contrast to MAb mu5.5. Maeda *et al.* [1992]
- 0.5beta: Chimeric mouse-human MAb Cbeta1 was constructed by combining the human Cgamma1 and Ckappa constant regions with the 0.5beta murine MAb – ADCC and neutralizing activity. Matsushita *et al.* [1992] (**complement**)
- 0.5beta: Potent neutralizing activity. D'Souza *et al.* [1991]
- 0.5beta: Emergence of virus resistant to MAb 0.5beta and autologous sera neutralization in IIIB infected chimps. Nara *et al.* [1990] (**escape**)
- 0.5beta: Type-specific neutralization of IIIB – does not neutralize MN or RF. Matsushita *et al.* [1988]; Skinner *et al.* [1988b] (**antibody generation**)

No. 557

Mab ID Cβ1, 0.5β

HXB2 Location gp160 (311–324)

Author Location gp120 (316–330 HXB2)

Epitope RGPGRFVTIGKIG

Subtype B

Neutralizing L

Immunogen vaccine

Vector/Type: protein Strain: B clade IIIB

HIV component: Env

Species (Isotype) humanized mouse (IgG1)

Ab Type gp120 V3

References Eda *et al.* 2006b; Ferrantelli & Ruprecht 2002; Kimura *et al.* 2002; Matsushita *et al.* 1992; Emini *et al.* 1992

- Cbeta1: This Ab was shown not to neutralize HIV-1 AD8, SHIV 89.6 and SHIV C2/1 Eda *et al.* [2006b]
- Cbeta1: Review of passive immunoprophylaxis with human NABs that also includes this chimeric mouse-human MAb, noting it protected 2/2 Chimpanzees from HIV-1 IIIB infection in the Emini *et al.* study published in 1992. Ferrantelli & Ruprecht [2002]
- Cbeta1: Defines epitope as IQRGPGRA – strong neutralizing activity against NL4-3 (X4 virus) and none against JRFL (R5 virus) – used as a control in a study of NAB activity in patients undergoing HAART. Kimura *et al.* [2002]
- Cbeta1: passive transfer to chimpanzees confers protection against challenge with homologous cell-free virus – mouse 0.5beta human IgG1 chimera. Emini *et al.* [1992]
- Cbeta1: Chimeric mouse-human MAb Cbeta1 was constructed by combining the human Cgamma1 and Ckappa constant regions with the 0.5beta murine MAb – ADCC and neutralizing activity. Matsushita *et al.* [1992]

No. 558

Mab ID C25

HXB2 Location gp160 (312–315)

Author Location (MOKW)

Epitope GPGR

Subtype B

Neutralizing P

Immunogen vaccine

Vector/Type: peptide Strain: B clade, B clade MN, B clade RF, Other HIV component: V3 Adjuvant: Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

Species (Isotype) mouse (IgG)

Ab Type gp120 V3

Research Contact Shuzo Matsushita, Kumamoto University, Japan shuzo@kaiju.medic.kumamoto-u.ac.jp

References Eda *et al.* 2006b

Keywords antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, binding affinity, variant cross-recognition or cross-neutralization

- C25: A new humanize MAb recognizing the V3 tip sequence was generated by transferring the genes of the complementary determining region of the mouse NAb C25 into genes of a human V region. C25 was raised by serial vaccinations of a C3H/HeN mouse with distinctive six B clade V3 loop peptides. KD-247 was shown to neutralize laboratory and primary isolates of CXCR4 and CCR5 viruses that possess a GPGR sequence in the Env V3 tip region more effectively than any of the reference Abs used in the study. Eda *et al.* [2006b] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, binding affinity, antibody sequence variable domain**)

No. 559

Mab ID 447-52D (447/52-DII, 447-52-D, 447d, 447-52-D, 447-D, 447, 447D)

HXB2 Location gp160 (312–315)

Author Location gp120 (MN)

Epitope GPXR

Subtype B

Neutralizing L P

Immunogen HIV-1 infection

Species (Isotype) human (IgG3λ)

Ab Type gp120 V3

Research Contact Dr. Susan Zolla-Pazner, NYU Med Center NY, NY; Veteran Affairs Med Center NY, NY; or Cellular Products Inc, Buffalo, NY,

References Haynes *et al.* 2006; Cham *et al.* 2006; Chakraborty *et al.* 2006; Holl *et al.* 2006a; Pantophlet *et al.* 2007; Nelson *et al.* 2007; Law *et al.* 2007; Kraft *et al.* 2007; Dhillon *et al.* 2007; Holl *et al.* 2006b; Haynes & Montefiori 2006; Eda *et al.* 2006b; Selvarajah *et al.* 2005; Pinter *et al.* 2005; Martín-García *et al.* 2005; Lusso *et al.* 2005; Krachmarov *et al.* 2005; Haynes *et al.* 2005; Gorny *et al.* 2005; Sharpe *et al.* 2004; Pugach *et al.* 2004; Pinter *et al.* 2004; Pantophlet *et al.* 2004; McCaffrey *et al.* 2004; Ling *et al.* 2004; Gorny *et al.* 2004; Binley *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Kessler *et al.* 2003; Binley *et al.* 2003; Pognard *et al.* 2003; Ferrantelli & Ruprecht 2002; He *et al.* 2002; Gorny *et al.* 2002; Sharon *et al.* 2002;

Srivastava *et al.* 2002; Verrier *et al.* 2001; York *et al.* 2001; Park *et al.* 2000; Nyambi *et al.* 2000; Ly & Stamatatos 2000; Hioe *et al.* 2000; Grovit-Ferbas *et al.* 2000; Gorny *et al.* 2000; Beddows *et al.* 1999; Hioe *et al.* 1999; Nyambi *et al.* 1998; Gorny *et al.* 1998; Connor *et al.* 1998; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Parren *et al.* 1998a; Smith *et al.* 1998; Mondor *et al.* 1998; Inouye *et al.* 1998; Ugolini *et al.* 1997; Gorny *et al.* 1997; Hill *et al.* 1997; Parren *et al.* 1997b; Boots *et al.* 1997; Hioe *et al.* 1997b; Hioe *et al.* 1997a; Fouts *et al.* 1997; Binley *et al.* 1997a; D'Souza *et al.* 1997; Sattentau 1996; Trkola *et al.* 1996a; Jagodzinski *et al.* 1996; Forthal *et al.* 1995; Moore & Ho 1995; Moore *et al.* 1995a; Zolla-Pazner & Sharpe 1995; Zolla-Pazner *et al.* 1995; Sattentau *et al.* 1995; Saarloos *et al.* 1995; Fontenot *et al.* 1995; Sattentau 1995; Moore *et al.* 1994a; Gorny *et al.* 1994; VanCott *et al.* 1994; Laal *et al.* 1994; Conley *et al.* 1994a; Spear *et al.* 1993; Cavacini *et al.* 1993a; Keller *et al.* 1993; Gorny *et al.* 1993; Karwowska *et al.* 1992b; Buchbinder *et al.* 1992; Gorny *et al.* 1992

**Keywords** acute/early infection, ADCC, antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, binding affinity, co-receptor, complement, dendritic cells, enhancing activity, escape, kinetics, mimotopes, neutralization, review, structure, subtype comparisons, Th2, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization, viral fitness and reversion

- 447-52D: This Ab was used to help define the antigenic profile of envelopes used in serum depletion experiments to attempt to define the neutralizing specificities of the broadly cross-reactive neutralizing serum. Peptides containing epitopes for 447-52D did not inhibit neutralization by broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals, indicating that the V3 epitope for this MAb did not account for the broad neutralizing activity observed. 447-52D bound to JR-FL and JR-CSF gp120 monomers but not to core JR-CSF gp120 monomer. Dhillon *et al.* [2007] (**antibody binding site definition and exposure, neutralization**)
- 447-52D: Viruses from early and late infection of a macaque with SHIV SF162P4 were resistant to contemporaneous serum that had broadly reactive NAbS. SF162 was highly susceptible to neutralization by anti-V3 MAbs 447D and P3E1, as well as anti-V1 MAb P3C8, while envelopes cloned from this animal at 304 days and at 643 days (time of death) post infection had developed resistance to all three of these antibodies. Kraft *et al.* [2007] (**neutralization, escape**)
- 447-52D: G1 and G2 recombinant gp120 proteins, consisting of 2F5 and 4E10, and 4E10 epitopes, respectively, engrafted

into the V1/V2 region of gp120, were tested as an immunogen to see if they could elicit MPER antibody responses. Deletion of V1/V2 from gp120, or its replacement with G1 and G2 grafts, did not greatly affect binding of 447-52D to gp120. Shortening of the N and C termini of the V3 loop enhanced the binding of 447-52D. Law *et al.* [2007] (**vaccine antigen design**)

- 447-52D: Z13e1, a high affinity variant of Fab Z13, was identified through targeted mutagenesis and affinity selection against gp41 and an MPER peptide. Z13e1 showed 100-fold improvement in binding affinity for MPER antigens over Z13. 447-52D was used as a control in this study. 447-52D was shown to clearly bind to monomers of gp120-gp41 while trimer binding was negligible, in accordance with its modest neutralization potency against HIV-1 JR-FL. Nelson *et al.* [2007] (**vaccine antigen design**)
- 447-52D: In this study the neutralization breadth of F425 B4e8 was assessed using a panel of 40 primary HIV-1 isolates, and 447-52D was found to have a similar profile, and was used as a control to gauge the effects of the amino acid substitutions in the V3 region. As expected, replacing Arg 315 with Ala or Gln and Pro 313 with Ala reduced binding affinity of this 447-52D substantially. Ala substitutions of residues in positions 304-309 and 319-320 also unexpectedly resulted in diminished binding affinity of the Ab. Pantophlet *et al.* [2007] (**antibody binding site definition and exposure, subtype comparisons**)
- 447-52D: Guinea-pigs were immunized with 447-52D epitope inserted at three different surface V3 loop locations in the small Escherichia coli Trx protein in order to generate a competent immunogen. Only one complex was shown to successfully generate anti-V3 Abs capable of out-competing 447-52D binding to gp120 and recognizing the same epitope as this Ab. However, these 447-52D-like Abs were not able to affect neutralization of JRFL and BAL. Chakraborty *et al.* [2006] (**neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization, binding affinity**)
- 447-52D: Cloned Envs (clades A, B, C, D, F1, CRF01\_AE, CRF02\_AG, CRF06\_cpx and CRF11\_cpx) derived from donors either with or without broadly cross-reactive neutralizing antibodies were shown to be of comparable susceptibility to neutralization by 447-52D. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 447-52D: The neutralization potency of this Ab against 7 HIV-1 primary isolates was compared to the neutralization potency of the anti-V3 MAb KD-247. Same Ab concentrations were needed for neutralization of the MN, N-NIID, and 92TH022 isolates, while higher concentrations of 447-52D were needed for the neutralization of the rest of the HIV-1 isolates suggesting KD-247 is more potent. Eda *et al.* [2006b]
- 447-52D: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design

strategies are also discussed. Haynes & Montefiori [2006] (**neutralization**)

- 447-52D: 29 subtype B V3 peptides were designed and used for immunization of guinea pigs. Peptides that induced Abs that neutralized more than 3 HIV isolates were shown to bind to this Ab better than peptides unable to induce neutralization of any of the HIV-1 primary isolates. Haynes *et al.* [2006] (**neutralization, binding affinity**)
- 447-52D: Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in iMDDCs was evaluated. The neutralizing activity of 447-52D was observed to be higher in iMDDCs than in PBLs and PHA-stimulated PBMCs. A 90% reduction of HIV infection was observed without induction of MDDC maturation by this mAb. It was also demonstrated that binding of this mAb to HIV-1 was necessary for inhibition of iMDDC infection. Increased expression of FcγRI on iMDDCs increased inhibition of HIV by 447-52D, suggesting the involvement of this receptor in the HIV-inhibitory activity of this mAb. Holl *et al.* [2006b] (**neutralization, dendritic cells**)
- 447-52D: The ability of this Ab to inhibit viral growth was increased when macrophages and immature dendritic cells (iDCs) were used as target cells instead of PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**dendritic cells**)
- 447-52d: 2909 is a human anti-Env NAb that was selected by a neutralization assay and binds to the quaternary structure on the intact virion. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670, 1418, nor 2G12. Gorny *et al.* [2005]
- 447-52D: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 447-52D has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)
- 447-52D: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Neutralization by anti-V3 B clade specific MAbs 447-52D and 4117C was fully blocked by a clade V3 loop fusion protein, but not an A clade fusion protein, while Cameroonian sera neutralization was fully blocked by both A and B clade fusion proteins. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 447-52D: The epitope for the MAb D19 is conserved and embedded in V3. D19 is unique in that for R5 viruses, it was cryptic and did not bind without exposure to sCD4, and for X4 and R5X4 isolates it was constitutively exposed. It had an overlapping binding region with MAbs 447-52D, B4e8, and 268-D, but different reactivity patterns and fine specificity. While B4e8 and 447-52D could bind to the R5 virus BaL in the absence of sCD4, treatment with sCD4 did increase the binding of both B4e8 and 447-52D, but did not impact their ability to neutralize BaL. Lusso *et al.* [2005] (**antibody binding site definition and exposure**)
- 447-52D: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication in microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglial-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using CD4BS MAbs F105 and IgG1b12, glycan-specific 2G12, and V3-specific 447-52D, and were unchanged. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Martín-García *et al.* [2005] (**antibody binding site definition and exposure**)
- 447-52D: This study is about the V2 MAb C108g, which is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potentially neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MAbs 4117c, 2219, 2191, and 447-52D (447-52D was the only one of the 4 V3 MAbs that could neutralize the unmodified JRFL); but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
- 447-52D: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V3 MAbs (447-52D, 19b, F245-B4e8 and 39F) bound to the GDMR antigen, but either did not bind or had diminished binding to mCHO. Selvarajah *et al.* [2005] (**vaccine-specific epitope characteristics, Th2**)
- 447-52D: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. Neutralization outside of the B clade was very rare, and seemed to depend on the presence of a GPGR V3 tip, which is rare outside of the B clade. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

- 447-52D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally sensitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Although 447-52D was selected using a peptide, it has conformational characteristics. Inter-clade cross-neutralization by anti-V3 conformation-dependent MAbs is reduced. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, review**)
- 447-52D: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides, but was an exception in that it is cross-neutralizing. 447-52D neutralized 12/13 clade B viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 447-52D: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of the V3 MAbs 694-98D and 447-52D, that both bind near the tip of the loop, was decreased by both thrombin and trypsin. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 447-52D: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of any of three glycans within or adjacent to the V3 loop (GM299 V3), C2 (GM292 C2), C3 (GM329 C3) increased neutralization susceptibility to 447-52D, but C4 (GM438 C4) or V5 (GM454 V5) removal did not make SF162 more sensitive. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure, vaccine antigen design**)
- 447-52D: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 447-52D. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 447-52D: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MAbs, including 447-52D, had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigppgrafyTtgE for JR-FL and TigppgrafyAtgD for SF162). Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 447-52D: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. 447-52D did not neutralize the primary or passaged variant. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization, viral fitness and reversion**)
- 447-52D: Analysis of the conformation of 447-52D in complex with the V3MN18 peptide (gp12 aa 310-329, KRKRI-HIGPGRAFYTTKN) was undertaken using solid state NMR. The bound peptide had a well defined constrained structure that was in good agreement with solution NMR and crystallographic studies. Sharpe *et al.* [2004] (**structure**)
- 447-52D: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. 447-52D was able to neutralize the SOS protein better than the wildtype, but did not neutralize SOS well when added post-attachment, as the V3 loop is involved in co-receptor engagement. Binley *et al.* [2003] (**vaccine antigen design**)
- 447-52D: The Fv fragment (composed of just the light and heavy variable regions, and the smallest intact binding unit of an Ab) of 447-52 D was expressed and purified. Preliminary NMR with the peptide epitope indicates that an NMR structure determination is feasible. Kessler *et al.* [2003] (**antibody sequence variable domain, structure**)
- 447-52D: This paper attempts to engineer a gp120 molecule that would focus the immune response onto the IgG1b12 epitope. Adding a glycosylation sequon (P313N) to the V3 loop knocked out binding to anti-V3 MAbs loop 2, 19b and 447-52-D. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 447-52D: Virion capture assays are not a good predictor of neutralization, and the presentation of epitopes using this assay seems to be different from that of functional Envelope spikes on primary isolates – F105 and b6 could efficiently

block the b12-mediated capture of infectious virions in a virus capture, but did not inhibit b12 neutralization – Ab 447-52D was able to potently neutralize 89.6 and to neutralize JR-CSF at a high concentration but poorly neutralized ADA – b12 was potent at neutralizing the three primary virions JR-CSF, ADA, and 89.6, but anti-V3 Abs 447-52D and 19b, which did not neutralize JR-CSF and ADA, captured amounts of p24 equal to or higher than the amounts captured by the neutralizing Ab b12. Poignard *et al.* [2003] (**antibody binding site definition and exposure, assay development, variant cross-recognition or cross-neutralization**)

- 447-52D: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 447-52D: Review of NAb. Ferrantelli & Ruprecht [2002]
- 447-52D: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 447-52D bound to primary isolates from all clades except CRF01 (E), was conformationally sensitive and showed the some of the most potent neutralizing activity. Gorny *et al.* [2002] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS), 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- 447-52D: The feasibility of determining the NMR structure of the V3(MN) peptide bound to the 447-52D Fab fragment was tested and a general strategy for obtaining NMR structures of V3 peptide-Fab fragments developed – preliminary NMR spectra for 447-52D complexed to a 23 amino acid V3 peptide was obtained. Sharon *et al.* [2002] (**structure**)
- 447-52D: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent—antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs—447-D recognized the gp120 monomer much more readily than o-gp140, suggesting the V3 loop is less exposed on o-gp140 and on intact virions. Srivastava *et al.* [2002] (**antibody binding site definition and exposure, vaccine antigen design**)
- 447-52D: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions, variant cross-recognition or cross-neutralization**)
- 447-52D: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAb alters some step after binding – the dissociation constant, Kd of 447-52D for the cell associated primary and TCLA Envs was equal, 3nM. York *et al.* [2001] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, binding affinity**)
- 447-52D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V3 MAbs 447-52D, 838-D, and 1334 bound with a 7-10 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 447-52D: To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**vaccine antigen design**)
- 447-52D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – V3 MAbs 447-52-D and 268-10-D did not effect proliferation. Hioe *et al.* [2000]
- 447-52D: Called 447D – SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral en-

- try. Ly & Stamatatos [2000] (**antibody binding site definition and exposure**)
- 447-52D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 447-52D showed the highest cross-reactivity, bound to 24/26 viruses tested, but achieved 90% neutralization only against MN, 50% against CA5, and no neutralization was observed for 3 other isolates tested. Nyambi *et al.* [2000] (**subtype comparisons**)
  - 447-52D: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000] (**antibody binding site definition and exposure**)
  - 447-52D: rgp120 derived from a R5X4 subtype B virus, HIV-1 W61D, was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs – TCLA strains showed enhanced 447-52D neutralization sensitivity relative to PBMC-adapted lines (32X increase between HIV-1 (M2424/PBMC(p0)) and HIV-1 (M2424/H9(p9)) and a >128X increase between HIV-1 (W61D/PBMC) and HIV-1 (W61D/SupT1) isolates) Beddows *et al.* [1999] (**variant cross-recognition or cross-neutralization**)
  - 447-52D: The presence of leukocyte function-associated molecule 1 (LFA-1) promotes virus infectivity and hinders neutralization, and anti-LFA-1 MAbs can enhance the neutralizing effect of anti-HIV V3 MAb 447-52D and anti-HIV CD4BS MAb IgG1b12 – non-neutralizing anti-HIV CD4BS MAb 654-D did not become neutralizing in the presence of anti-LFA-1 MAbs. Hioe *et al.* [1999]
  - 447-52D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a] (**review, subtype comparisons**)
  - 447-52D: MAb peptide-reactivity pattern clustered with the immunological related MAbs: 1334, 419, 504, 447, 453 and 537 – the core amino acids GP tended to be critical for reactivity in this group – 447 reacted with peptides containing GPGR, but also with many lacking this sequence (GPGQ, for example), and it failed to react with 2/14 peptides containing GPGR, illustrating the importance of context. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 447-52D: Ab from gp120 vaccinated individuals prior to infection, who subsequently became HIV infected, could not achieve 90% neutralization of the primary virus by which the individuals were ultimately infected – these viruses were not particularly refractive to neutralization, as determined by their susceptibility to neutralization by MAbs 2G12, IgG1b12, 2F5 and 447-52D. Connor *et al.* [1998]
  - 447-52D: Kinetic parameters were measured, and the association rates were similar, but dissociation rate constants were quite variable for V3 MAbs, 1324E was comparable to 447-52D. Gorny *et al.* [1998] (**kinetics**)
  - 447-52D: Called 447-D – 447-D resistance took longer to acquire in virus with the M184V substituted RT, and had the form (AAC N to TAC Y) at position 5 of the V3 loop, rather than the GPGR to GPGR resistance found with wildtype RT. Inouye *et al.* [1998]
  - 447-52D: Inhibits binding of Hx10 to both CD4 positive and negative HeLa cells. Mondor *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
  - 447-52D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – 447-52D was the most potent and cross-reactive of 18 human MAbs tested and was the only MAb which bound to virions from isolates CA20 (subtype F), CA13 (subtype H), and VI526 (subtype G) Nyambi *et al.* [1998] (**subtype comparisons**)
  - 447-52D: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
  - 447-52D: Called 447-52-D – The tip of the MN V3 loop was inserted into cold causing human rhinovirus 14 (HRV14) – chimeras were immunoselected, and chimeric viruses were neutralized by anti-V3 loop antibodies, and 447-52D was among the Abs used – chimeric viruses elicited potent NAb in guinea pigs against ALA-1 and MN. Smith *et al.* [1998] (**vaccine antigen design**)
  - 447-52D: Abs that recognize discontinuous epitopes can identify mimotopes from a phage peptide display library – 447-52D has an epitope involving the tip of the V3 loop, that was previously studied with this method Keller *et al.* [1993] – in Keller *et al.*, with no competition, LxGPxR was the most common six-mer, 38% of the peptides – after competition with a gp120 IIIB ligand (QRGPGR)<sub>i</sub>, RGPxR was the most common and one peptide had the sequence QRGPGR, showing type specific mimotopes can be enriched by strain specific ligand and competition protocols Boots *et al.* [1997]. Boots *et al.* [1997]; Keller *et al.* [1993] (**antibody binding site definition and exposure, mimotopes**)
  - 447-52D: In a multilaboratory blinded study, failed to consistently neutralize any of nine B clade primary isolates – many of these isolates had the GPGR motif at the apex of the V3 loop. D'Souza *et al.* [1997] (**variant cross-recognition or cross-neutralization, assay standardization/improvement**)
  - 447-52D: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 447-52D bound monomer, oligomer, and neutralized JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
  - 447-52D: Used as a control for comparison to five V3 RF selected antibodies – 447-52D was reactive with A, B, and C clade peptides, but not E. Gorny *et al.* [1997] (**subtype comparisons**)
  - 447-52D: Called 447 – gp120 can inhibit MIP-1alpha from binding to CCR5, but this inhibitory effect is blocked by pre-incubation of gp120 with three anti-V3 MAbs: 447, 257, 1027 – MAb 670 which binds in the C5 region had no effect. Hill *et al.* [1997] (**co-receptor**)

- 447-52D: Tested using a resting cell neutralization assay. Hioe *et al.* [1997a] (**assay standardization/improvement**)
- 447-52D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Neutralizes TCLA strains but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Viral binding inhibition by 447-D was correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997] (**antibody binding site definition and exposure**)
- 447-52D: Called 447-52-D – The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – CRDS inhibits 447-52D binding. Jagodzinski *et al.* [1996] (**antibody binding site definition and exposure**)
- 447-52D: Review: called 447-52-D – only four epitopes have been described which can stimulate a useful neutralizing response to a broad spectrum of primary isolates, represented by the binding sites of MAbs: 447-52-D, 2G12, Fab b12, and 2F5. Sattentau [1996] (**variant cross-recognition or cross-neutralization, review**)
- 447-52D: Neutralizes JR-FL – strongly inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**co-receptor, variant cross-recognition or cross-neutralization**)
- 447-52D: Called 447 – The tip of the V3 loop was presented in a mucin backbone – higher valency correlates with stronger affinity constant. Fontenot *et al.* [1995] (**vaccine antigen design**)
- 447-52D: Neutralizing (- complement), no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC, complement, enhancing activity**)
- 447-52D: Binding affected by identity of amino acids flanking GPGR core – poor breadth of primary virus neutralization. Moore *et al.* [1995a] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Review: the V3 loop motif GPGR is not common outside subtype B isolates, MAb 19b is more cross-reactive than 447-52D. Moore & Ho [1995] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Ab-mediated activation of complement on HIV+ cells is higher than Ab independent activation—what has been termed “Ab independent” in fact results in part from IgM in normal human serum that is HIV-cross-reactive. Saarloos *et al.* [1995] (**complement**)
- 447-52D: Called 447d – Formalin inactivation of virus at 0.1% formalin for 10 hours at 4 degrees was optimal for inactivation of virus while maintaining epitope integrity. Sattentau *et al.* [1995] (**vaccine antigen design**)
- 447-52D: Serotyping study using flow-cytometry – bound only to GPGR V3 loop tips. Zolla-Pazner *et al.* [1995] (**antibody binding site definition and exposure**)
- 447-52D: Neutralization of primary and prototype laboratory HIV-1 isolates using a resting cell assay enhances sensitivity. Zolla-Pazner & Sharpe [1995] (**assay development, variant cross-recognition or cross-neutralization**)
- 447-52D: Requires GPxR at the tip of the V3 loop, common in B clade – neutralized primary isolates. Conley *et al.* [1994a] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 447-52D: Mild oxidation of carbohydrate moieties does not alter binding. Gorny *et al.* [1994] (**antibody binding site definition and exposure**)
- 447-52D: Neutralization synergy in combination with CD4 binding domain MAbs. Laal *et al.* [1994] (**antibody interactions**)
- 447-52D: Competition studies with human sera from seroconverting individuals showed that anti-CD4 BS antibodies can arise very early in infection, comparable or prior to anti-V3 antibodies. Moore *et al.* [1994a] (**acute/early infection**)
- 447-52D: GPGQ in MAL resulted in enhanced dissociation – GPGQ in CM234 or K14T did not bind – binding affected by identity of amino acids flanking GPGR core. VanCott *et al.* [1994] (**antibody binding site definition and exposure**)
- 447-52D: Additive neutralization of MN and SF2 when combined with CD4 binding site MAb F105 – supra-additive neutralization of RF. Cavacini *et al.* [1993a] (**antibody interactions**)
- 447-52D: Neutralizes MN and IIIB: GPGR, and binds SF2: GPGR. Gorny *et al.* [1993] (**variant cross-recognition or cross-neutralization**)
- 447-52D: Peptide phage library showed that any of the residues ADGLMNQRS in the X position tolerated in peptides that react well with the antibody. Keller *et al.* [1993] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 447-52D: Complement mediated virolysis of IIIB, but not in the presence of sCD4. Spear *et al.* [1993] (**complement**)
- 447-52D: 60-fold increase in neutralization potency when combined 1:1 with human MAb 588-D. Buchbinder *et al.* [1992] (**antibody interactions**)
- 447-52D: Requires GPXR at the tip of the V3 loop – neutralizes a broad array of B clade lab isolates. Gorny *et al.* [1992] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 447-52D: Reacts with MN, NY5, CDC4, SF2, RF, WM52, and HXB2. Karwowska *et al.* [1992b] (**variant cross-recognition or cross-neutralization**)

No. 560

MAb ID NM-01 (hNM01, hNM-01)

HXB2 Location gp160 (312–315)

Author Location gp120 (MN)

Epitope GPGR

Neutralizing L



**Immunogen** vaccine

*Vector/Type:* human rhinovirus 14 *Strain:*  
B clade MN *HIV component:* V3

**Species (Isotype)** mouse (IgG)**Ab Type** gp120 V3**Research Contact** M. Terada, Jason Grabely

**References** Zwick *et al.* 2003; Nakamura *et al.* 2000; Smith *et al.* 1998; Yoshida *et al.* 1997; Ohno *et al.* 1991

**Keywords** antibody interactions, complement, immunotherapy

- NM-01: Called hNM01. scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. The humanized version of this MAb was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- NM-01: Called hNM01. The CDR region of the murine MAb NM-01 was put into a human IgG frame. The epitope recognition was preserved, but the neutralizing potency of the humanized form was enhanced. It could activate complement. Nakamura *et al.* [2000] (**complement, immunotherapy**)
- NM-01: The tip of the MN V3 loop was inserted into cold-causing human rhinovirus 14 (HRV14) – chimeras were immunoselected, and chimeric viruses were neutralized by anti-V3 loop antibodies, and NM-01 was among the Abs used – chimeric viruses elicited potent NAb in guinea pigs against ALA-1 and MN. Smith *et al.* [1998]
- NM-01: Resistance mutation selected by propagation of molecular cloned isolate in the presence of NM-01. Yoshida *et al.* [1997]

No. 561

**MAb ID** 1026**HXB2 Location** gp160 (312–317)**Author Location** gp120 (MN)**Epitope** GPGRAPH**Neutralizing** L**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG)**Ab Type** gp120 V3

**References** Bou-Habib *et al.* 1994; Nakamura *et al.* 1993

- 1026: Greater affinity for T cell-tropic strain T-CSF, derived from JR-CSF, than to the primary isolate JR-CSF. Bou-Habib *et al.* [1994]
- 1026: Bound diverse strains, neutralizing activity against MN, close to GPGRAPH. Nakamura *et al.* [1993]

No. 562

**MAb ID** 1034**HXB2 Location** gp160 (312–317)**Author Location** gp120 (MN)**Epitope** GPGRAPH**Neutralizing** L**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade MN  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG)**Ab Type** gp120 V3

**References** Berman *et al.* 1997; Bou-Habib *et al.* 1994

- 1034: Binds to 5/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997]
- 1034: Greater affinity for T cell tropic T-CSF, derived from JR-CSF, than to the primary isolate JR-CSF, close to GPGRAPH. Bou-Habib *et al.* [1994]

No. 563

**MAb ID** 59.1 (R/V3-59.1)**HXB2 Location** gp160 (312–317)**Author Location** gp120 (308–313 MN)**Epitope** GPGRAPH**Neutralizing** L**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade MN  
*HIV component:* V3

**Species (Isotype)** mouse (IgG1)**Ab Type** gp120 V3

**Research Contact** Mary White-Scharf and A. Profy, Repligen Corporation

**References** York *et al.* 2001; Stanfield *et al.* 1999; Smith *et al.* 1998; Ghiara *et al.* 1997; Seligman *et al.* 1996; D'Souza *et al.* 1994; Bou-Habib *et al.* 1994; Ghiara *et al.* 1993; Potts *et al.* 1993; White-Scharf *et al.* 1993; D'Souza *et al.* 1991

- 59.1: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAb alters some step after binding. York *et al.* [2001]
- 59.1: The crystal structure of V3 loop peptides bound to Fabs was obtained – conformational changes in the tip of the V3 loop (GPGR) were observed when different MAbs were bound. Stanfield *et al.* [1999]
- 59.1: The tip of the MN V3 loop was inserted into cold-causing human rhinovirus 14 (HRV14) – chimeras were immunoselected, and chimeric viruses were neutralized by anti-V3 loop antibodies, and 59.1 was among the Abs used – chimeric viruses elicited potent NAb in guinea pigs against ALA-1 and MN. Smith *et al.* [1998]
- 59.1: A conformationally restricted analog of the tip of the V3 loop was constructed and bound with Fab 59.1 – crystal structure shows interactions between 59.1 and an MN peptide and 59.1 and the modified peptide are similar, but NMR studies reveal that the modified peptide is more ordered in solution, retaining the Fab bound form. Ghiara *et al.* [1997]

- 59.1: Competition ELISAs with serial deletions produced longer estimate of epitope length than x-ray crystallography or Alanine substitution, RIHIGPGRAFYTT, suggesting significance of non-contact residues. Seligman *et al.* [1996]
- 59.1: Greater affinity for T-cell tropic strain T-CSF than the primary isolate JR-CSF, from which T-CSF was derived. Bou-Habib *et al.* [1994]
- 59.1: Multi-lab study for antibody characterization and assay comparison – neutralizes MN and IIIB. D'Souza *et al.* [1994]
- 59.1: Crystal structure of a 24 amino acid peptide from the V3 loop bound to 59.1 Fab fragment – contact residues IGP-GRAF. Ghiara *et al.* [1993]
- 59.1: Synergistic neutralization of MN when combined with sCD4 or the CD4BS MAb F105. Potts *et al.* [1993]
- 59.1: Epitope defined by peptide reactivity and binding affinity with amino acid substitutions – GPGRAF. White-Scharf *et al.* [1993]
- 59.1: Called R/V3-59.1 – potent neutralizing MAb. D'Souza *et al.* [1991]

No. 564

MAb ID polyclonal

HXB2 Location gp160 (312–317)

Author Location gp120 (316–321)

Epitope GPGRAF

Neutralizing

Immunogen vaccine

Vector/Type: protein, polyepitope HIV component: gp160 Adjuvant: BSA

Species (Isotype) rabbit

Ab Type gp120 V3

References Lu *et al.* 2000b; Lu *et al.* 2000c

- High titer response to ELDKWA and RILAVERYLKD was observed upon vaccination with multiple-epitope vaccine CG-GPGRAFY-G-ELDKWA-G-RILAVERYLKD conjugated to BSA, a weak response to GPGRAFY – immunization with CG-(ELDKWA-GPGRAFY)<sub>2</sub>-K was also tried, yielding a strong Ab response to ELDKWA, weak to GPGRAF – gp160 vaccination yielded strong Ab response but not to any of the peptides studied here. Lu *et al.* [2000c,b]

No. 565

MAb ID 10E3

HXB2 Location gp160 (312–318)

Author Location gp120 (317–323 IIIB)

Epitope GPGRAFY

Neutralizing

Immunogen vaccine

Vector/Type: peptide keyhole limpet hemocyanin (KLH) conjugate Strain: B clade IIIB HIV component: V3

Species (Isotype) mouse (IgG)

Ab Type gp120 V3

References Li *et al.* 2002; Tian *et al.* 2001

Keywords vaccine antigen design

- 10E3: A polyepitope vaccine was designed based on a recombinant GST fusion protein containing three repeats of the 2F5 core epitope ELDKWA combined with the V3 region peptide GPGRAFY. Abs raised in mice could recognize the peptides,

sgp41, and CHO-WT cells that expressed HIV-1 Env on their surface. Li *et al.* [2002] (**vaccine antigen design**)

- 10E3: Peptides GPGRAFY and ELDKWAG were conjugated to KLH and used to raise mouse monoclonal Ab – MAb hybridomas were generated with defined specificity – 10E3 binds to the peptide GPGRAFY and to rgp160. Tian *et al.* [2001]

No. 566

MAb ID polyclonal

HXB2 Location gp160 (312–318)

Author Location gp120 (317–323)

Epitope GPGRAFY

Neutralizing

Immunogen vaccine

Vector/Type: peptide HIV component: V3 Adjuvant: BSA

Species (Isotype) rabbit, mouse

Ab Type gp120 V3

References Yu *et al.* 2000

- High levels of epitope-specific Abs were induced by the peptide-BSA conjugates C-(GPGRAF)<sub>4</sub>-BSA or C-(TRPNNNTRKSIRIQRGPGRAFYTIG KI)-BSA but not by rgp160 vaccine. Yu *et al.* [2000]

No. 567

MAb ID N11-20 (110-H)

HXB2 Location gp160 (312–320)

Author Location gp120 (317–325)

Epitope GPGRAFVTI

Neutralizing L (LAI)

Immunogen

Species (Isotype) mouse (IgG1κ)

Ab Type gp120 V3

Research Contact J. C. Mazie, Hybridolab, Institut Pasteur

References Valenzuela *et al.* 1998

- N11-20: Neutralization of LAI in CEM cells by anti-V3 MAbs 110.4 and N11-20 is through inhibition of virus binding to the cell. Valenzuela *et al.* [1998]

No. 568

MAb ID 5025A (5025)

HXB2 Location gp160 (313–317)

Author Location gp120 (313–317 BH10)

Epitope pgRAF

Neutralizing L

Immunogen vaccine

Vector/Type: peptide Strain: B clade BH10 HIV component: V3

Species (Isotype) mouse (IgG)

Ab Type gp120 V3

Research Contact Paul Durda, Du Pont de Nemours and Co

References D'Souza *et al.* 1991; Langedijk *et al.* 1991

- 5025: Called 5025 – strain specific weakly neutralizing. D'Souza *et al.* [1991]
- 5025A: Generation and fine mapping of murine MAbs. Langedijk *et al.* [1991]

No. 569

MAb ID N70-1.9b

HXB2 Location gp160 (313–318)

**Author Location** gp120 (316–322)  
**Epitope** PGRAFY  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1)  
**Ab Type** gp120 V3  
**References** Gorny & Zolla-Pazner 2004; Scott *et al.* 1990; Robinson *et al.* 1990a  
**Keywords** ADCC, review, variant cross-recognition or cross-neutralization

- N70-1.9b: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- N70-1.9b: Type specificity. Robinson *et al.* [1990a] (**variant cross-recognition or cross-neutralization**)
- N70-1.9b: Type specific neutralization, ADCC directed against MN infected cells. Scott *et al.* [1990] (**ADCC, variant cross-recognition or cross-neutralization**)

**No.** 570

**MAb ID** 902

**HXB2 Location** gp160 (313–324)

**Author Location** gp120 (IIIB)

**Epitope** PGRAFVTIGKIG

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* gp160

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** gp120 V3

**Research Contact** Bruce Chesebro, Rocky Mountain National Laboratory, Montana

**References** Ling *et al.* 2004; Sakaida *et al.* 1997; Earl *et al.* 1994; Broder *et al.* 1994; Laman *et al.* 1993; Chesebro & Wehrly 1988

**Keywords** antibody binding site definition and exposure

- 902: NIH AIDS Research and Reference Reagent Program: 522.
- 902: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of the V3 MAbs 694-98D and 447-52D, that both bind near the tip of the loop, was decreased by both thrombin and trypsin, 932 binding was only decreased by trypsin. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 902: V3-BH10 peptide with loop-structure inhibits IL-2 induced T-cell proliferation, thought to be due to altering intracellular signaling, and MAb 908 can block the peptide inhibition. Sakaida *et al.* [1997]
- 902: Epitope may be partially masked or altered in the oligomeric molecule. Broder *et al.* [1994]
- 902: Used as a control in a study of the influence of oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]
- 902: Strain specific neutralization of HIV. Chesebro & Wehrly [1988]

**No.** 571

**MAb ID** 694/98-D (694/98, 694.8, 694/98D)

**HXB2 Location** gp160 (314–317)

**Author Location** gp120 (IIIB)

**Epitope** GRAF

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1λ)

**Ab Type** gp120 V3

**Research Contact** Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu

**References** Ling *et al.* 2004; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zwick *et al.* 2003; Zhang *et al.* 2002; He *et al.* 2002; Edwards *et al.* 2002; Park *et al.* 2000; Nyambi *et al.* 2000; Altmeyer *et al.* 1999; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a; Schonning *et al.* 1998; Nyambi *et al.* 1998; Andrus *et al.* 1998; Li *et al.* 1998; Smith *et al.* 1998; Zolla-Pazner *et al.* 1997; Li *et al.* 1997; Forthal *et al.* 1995; Zolla-Pazner *et al.* 1995; Van-Cott *et al.* 1995; Cook *et al.* 1994; Van-Cott *et al.* 1994; Laal *et al.* 1994; Gorny *et al.* 1994; Spear *et al.* 1993; Cavacini *et al.* 1993a; Gorny *et al.* 1993; Gorny *et al.* 1992; Gorny *et al.* 1991; Skinner *et al.* 1988b

**Keywords** antibody binding site definition and exposure, antibody interactions, review, variant cross-recognition or cross-neutralization

- 694/98D: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 694/98-D: Called 694/98. V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using IIIB gp120. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 694-98D: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of the V3 MAbs 694-98D and 447-52D, that both bind near the tip of the loop, was decreased by both thrombin and trypsin. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 694/98D: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region,

- CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 694/98-D: Called 694/98D – Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002]
  - 694/98-D: Called 694 – Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS), 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
  - 694/98-D: A panel of 47 human MAbs was tested against 26 HIV-1 group M primary isolates from clades A through H – 19 V3 MAbs were tested, and of 494 combinations, 44% displayed some viral binding – V3 MAbs tended to have the most cross-reactive binding to clade A, B, C, and D isolates, less to E, F, G, and H – 694/98-D showed intermediate reactivity. Nyambi *et al.* [2000]
  - 694/98-D: Called 694/98D – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
  - 694/98-D: A Semliki Forest virus (SFV) expression system carrying BX08 env was used to study the conformation of gp120 – intracytoplasmic gp120 was recognized by the anti-V3 MAbs K24 and F5.5, while gp120 at the plasma membrane was detected only by conformation dependent MAbs 2G12, 670-D and 694/98D and not linear V3 MAbs – expression in rat brain also showed that surface-expressed Env was recognized only by the conformation-dependent antibodies and not by anti-V3 antibodies. Altmeyer *et al.* [1999]
  - 694/98-D: Review of clade specificity and anti-V3 HIV-1-Abs. Zolla-Pazner *et al.* [1999a]
  - 694/98-D: MAb peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b]
  - 694/98-D: Used to study pre- and post-exposure prophylaxis Hu-PBL-SCID mice infected by an intraperitoneal injection of HIV-1 LAI – MAb half-life in plasma in mice is 9 days – 2 hours post-694/98-D mice were challenged with LAI, and at an Ab concentration of 1.32 mg/Kg, 50% of the mice were infected – one of the infected mice carried the resistant form GRTF rather than GRAF (critical amino acids for binding are GRA) – post-exposure prophylaxis was effective if delivered 15 min post-exposure, but declined to 50% if delivered 60 min post-exposure, and similar time constraints have been observed for HIVIG, 2F5 and 2G12, in contrast to MAb BAT123 that could protect delivered 4 hours post infection. Andrus *et al.* [1998]
  - 694/98-D: Neutralization synergy was observed when the MAbs 694/98-D (V3), 2F5 (gp41), and 2G12 (gp120 discontinuous) were used in combination, and even greater neutralizing potential was seen with the addition of a fourth MAb, F105 (CD4 BS) Li *et al.* [1998]
  - 694/98-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – 694/98-D bound only to B and D clade virions and had limited cross reactivity. Nyambi *et al.* [1998]
  - 694/98-D: In a study of the influence of the glycan at position 306 of the V3 loop on MAb recognition, anti-V3 MAbs were found to neutralize an HIV-BRU mutant virus that lacks the V3 loop glycan more efficiently than HIV-BRU. Schonning *et al.* [1998]
  - 694/98-D: The tip of the MN V3 loop was inserted into cold causing human rhinovirus 14 (HRV14) – chimeras were immunoselected, and chimeric viruses were neutralized by anti-V3 loop antibodies, and 694/98-D was among the Abs used – chimeric viruses elicited potent NAb in guinea pigs against ALA-1 and MN. Smith *et al.* [1998]
  - 694/98-D: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – could only achieve 50% neutralization alone – all Ab combinations tested showed synergistic neutralization – 694/98-D has synergistic response with MAbs F105, 15e, b12, 2F5, 17b, 2G12, and 48d, and with HIVIG. Li *et al.* [1997]
  - 694/98-D: ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995]
  - 694/98-D: Human HIV-1 infected sera and MAb 694/98 have high reactivity to MN and RF infected H9 cells, but Genentech rec gp120 IIIB vaccine recipients do not. VanCott *et al.* [1995]
  - 694/98-D: Serotyping study using flow-cytometry – bound GRAX bearing virus in 10/11 cases – somewhat conformation dependent. Zolla-Pazner *et al.* [1995]
  - 694/98-D: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – V3 MAbs can inhibit gp120 binding to GalCer *in vitro* – binding of GalCer to gp120 inhibited but did not completely block MAb binding. Cook *et al.* [1994]
  - 694/98-D: 50% neutralization of HIV-IIIB at a concentration of 0.15µg/ml. Gorny *et al.* [1994]
  - 694/98-D: Potent neutralization of IIIB – no neutralization synergy in combination with CD4 binding domain MAbs. Laal *et al.* [1994]
  - 694/98-D: GRVY did not alter peptide binding – GRVI and GQAW enhanced dissociation – GQVF and GQAL did not bind. VanCott *et al.* [1994]
  - 694/98-D: Neutralizes MN and IIIB (GRAF) – binds SF2 (GRAF) – binding reactivity: MN, IIIB, SF2, NY5, RF, CDC4, WM52. Gorny *et al.* [1993]

- 694/98-D: Called 694-D – complement mediated virolysis of IIIB, but not in the presence of sCD4. Spear *et al.* [1993]
- 694/98-D: Type-specific lab isolate neutralization was observed – binds with 1-3 fold greater affinity to gp120 than to peptides. Gorny *et al.* [1992]
- 694/98-D: This MAb was first described here. Skinner *et al.* [1988b]

No. 572

MAb ID MO101/V3,C4

HXB2 Location gp160 (314–323)

Author Location gp120 (314–323)

Epitope GRAFVTIGKI+LGVAPTKAKR

**Neutralizing****Immunogen** *in vitro* stimulation or selection**Species (Isotype)** human (IgM)**Ab Type** gp120 V3-C4**References** Ohlin *et al.* 1992

- MO101: Generated in response to IIIB Env 286-467 upon *in vitro* stimulation of uninfected-donor lymphocytes – reacts with peptides 314-323 + 494-503 from the V3 and C4 regions. Ohlin *et al.* [1992]

No. 573

MAb ID MO101/V3,C4

HXB2 Location gp160 (314–323)

Author Location gp120 (314–323)

Epitope GRAFVTIGKI+LGVAPTKAKR

**Neutralizing****Immunogen** *in vitro* stimulation or selection**Species (Isotype)** human (IgM)**Ab Type** gp120 V3-C5**References** Ohlin *et al.* 1992

- MO101: Generated through *in vitro* stimulation of uninfected-donor lymphocytes with pB1 containing IIIB Env 286-467 – reacts with peptides from the V3 and C4 regions, positions 314-323 + 494-503, peptides GRAFVTIGKI + LGVAPTKAKR. Ohlin *et al.* [1992]

No. 574

MAb ID MO101/V3,C4

HXB2 Location gp160 (314–323)

Author Location gp120 (494–503)

Epitope GRAFVTIGKI+LGVAPTKAKR

**Neutralizing****Immunogen** *in vitro* stimulation or selection**Species (Isotype)** human (IgM)**Ab Type** gp120 V3-C5**References** Ohlin *et al.* 1992

- MO101: Generated through *in vitro* stimulation of uninfected-donor lymphocytes with pB1 containing IIIB Env 286-467 – reacts with peptides from the V3 and C4 regions, positions 314-323 + 494-503, peptides GRAFVTIGKI + LGVAPTKAKR. Ohlin *et al.* [1992]

No. 575

MAb ID 9205 (NEA-9205 NEA9205)

HXB2 Location gp160 (315–317)

Author Location gp120 (IIIB)

Epitope RAF

**Neutralizing L****Immunogen** vaccine*Vector/Type:* peptide *Strain:* B clade IIIB*HIV component:* V3**Species (Isotype)** mouse (IgG1)**Ab Type** gp120 V3**Research Contact** NEN, Boston MA, commercial**References** Huskens *et al.* 2007; Gram *et al.* 2002; Schonning *et al.* 1999; Schonning *et al.* 1998; Fontenot *et al.* 1995; VanCott *et al.* 1994; Allaway *et al.* 1993; Trujillo *et al.* 1993; Durda *et al.* 1990**Keywords** variant cross-recognition or cross-neutralization

- 9205 database comment: Also see MAb called 5023A.
- 9205: 2G12 cross-neutralization and escape was the emphasis of this study. The Mab 9205 was used as a control. 9205 did not bind to nor inhibit the strains NDK or HE, while it did neutralize NL43 and MN. Huskens *et al.* [2007] (**variant cross-recognition or cross-neutralization**)
- 9205: Called NEA9205 – gp120 capture ELISAs with MAbs D7324 (anti-C-term) or 9205 (anti-V3) were compared in a study of orientation of glycosylation sites – CD4 binding could only inhibit deglycosylation when gp120 was bound to the plate by D7324, not by 9205, while Abs from HIV-1 infected people inhibited deglycosylation most effectively when gp120 was caught by 9205. Gram *et al.* [2002]
- 9205: Called NEA-9205 – the stoichiometry of MAb neutralization was tested and the data indicated that binding for neutralization was incremental not all or none, i.e., each envelope oligomer binds a single MAb and each Env oligomer bound reduces the chances of infection – 9205 binds only to Env with a glycosylation site mutation in the V3 loop, A308T. Schonning *et al.* [1999]
- 9205: Called NEA-9205 – The N306 glycan of the V3 loop makes the tip of the V3 loop inaccessible to this MAb in oligomeric Env, loss of this glycan enhances neutralization sensitivity. Schonning *et al.* [1998]
- 9205: Neutralizes IIIB but not MN – significantly slower dissociation constant for IIIB than MN. VanCott *et al.* [1994]
- 9205: Synergy with combinations of CD4-based molecules in inhibition of HIV-1 Env mediated cell fusion. Allaway *et al.* [1993]
- 9205: Called NEA-9205, epitope RIQRGPGRAFVTIGK – reacts with three human brain proteins of 35, 55, 110 kd molecular weight – similar to 9284 – RAF is the core reactivity. Trujillo *et al.* [1993]

No. 576

MAb ID 110.1

HXB2 Location gp160 (316–322)

Author Location gp120 (316–322)

Epitope AFVTIGK

**Neutralizing L****Immunogen** vaccine*Vector/Type:* protein *HIV component:*

gp120

**Species (Isotype)** mouse**Ab Type** gp120 V3**Research Contact** F. Traincard, Pasteur Institute, France

- References** Parren *et al.* 1998a; Wyatt *et al.* 1997; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Moore *et al.* 1994c; Moore *et al.* 1993b
- 110.I: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
  - 110.I: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997]
  - 110.I: Reciprocal binding inhibition with other anti-V3 and anti-C4 MAbs – and enhances binding of some anti-V2 MAbs – binding enhanced by some anti-CD4 binding site MAbs. Moore & Sodroski [1996]
  - 110.I: Epitope suggested to be RAFVTIGK – V3 MAbs 9284, BAT123, 110.5, and 110.I could each significantly increase gp120 dissociation from virus, mimicking sCD4, and expose the gp41 epitope for MAb 50-69, in contrast to anti-V2 MAbs. Poignard *et al.* [1996a]
  - 110.I: Binds equally well to monomer and oligomer, rapid association and potent neutralization of lab strains. Sattentau & Moore [1995]
  - 110.I: Binds to carboxy-terminal side of the V3 loop – inhibits binding of C4 region MAb G3-299. Moore *et al.* [1993b]

No. 577

- MAb ID** anti-HIV-2 polyclonal  
**HXB2 Location** gp160 (317–320)  
**Author Location** gp120 (315–318 SBL6669 HIV-2)  
**Epitope** FHSQ+WCR  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* HIV-2 SBL6669-ISY *HIV component:* V3  
**Species (Isotype)** guinea pig (IgG)  
**Ab Type** gp120 V3  
**References** Morner *et al.* 1999
- Neutralizing Abs against HIV-2 V3 are produced when peptides spanning two non-contiguous parts of the V3 loop are used for vaccination including amino acids 315-318 near the tip (FHSQ) and 329-331 (WCR) at the C-term Cys. Morner *et al.* [1999]

No. 578

- MAb ID** B2C  
**HXB2 Location** gp160 (319–321)  
**Author Location** gp120 (HIV2ROD)  
**Epitope** HYQ  
**Subtype** HIV-2  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* HIV-2 ROD  
**Species (Isotype)** mouse  
**Ab Type** gp120 C3  
**References** Matsushita *et al.* 1995
- B2C: Viral neutralization was type-specific for HIV-2 ROD. HYQ is the core binding region. Matsushita *et al.* [1995]

No. 579

- MAb ID** IIIB-V3-01  
**HXB2 Location** gp160 (320–328)  
**Author Location** gp120 (IIIB)  
**Epitope** IGKIGNMRQ  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade IIIB  
*HIV component:* V3  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 V3  
**Research Contact** Jon Laman  
**References** Laman *et al.* 1993
- IIIB-V3-01: UK Medical Research Council AIDS reagent: ARP3046.
  - IIIB-V3-01: NIH AIDS Research and Reference Reagent Program: 1726.
  - IIIB-V3-01: Specific for carboxy-terminal flank of the IIIB V3 loop – epitope is hidden native gp120, exposed on denaturation. Laman *et al.* [1993]

No. 580

- MAb ID** D/6D1  
**HXB2 Location** gp160 (346–377)  
**Author Location** gp120 (351–382 LAI)  
**Epitope** ASKLREQFGNNKTIIFKQSSGGDPEIVTHSFN  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp120  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 V4  
**References** Bristow *et al.* 1994
- D/6D1: V4 MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp120 and rgp160. Bristow *et al.* [1994]

No. 581

- MAb ID** 2H1B  
**HXB2 Location** gp160 (357–362)  
**Author Location** gp120 (370–376 HIV2ROD)  
**Epitope** RNISFKA  
**Subtype** HIV-2  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* HIV-2 ROD  
**Species (Isotype)** mouse  
**Ab Type** gp120 C3  
**References** Matsushita *et al.* 1995
- 2H1B: Binds in WB, but binds poorly to Env on the cell surface. Matsushita *et al.* [1995]

No. 582

- MAb ID** 4D7/4  
**HXB2 Location** gp160 (360–380)  
**Author Location** gp120 (361–380 LAI)  
**Epitope** IFKQSSGGDPEIVTHSFNCGG  
**Subtype** B  
**Neutralizing**

**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 V4  
**Research Contact** S. Ranjbar, NIBSC, UK  
**References** Moore *et al.* 1994c  
 • 4D7/4: UK Medical Research Council AIDS reagent: ARP3051.  
 • 4D7/4: C3 region – the relative affinity for denatured/native gp120 is >10. Moore *et al.* [1994c]

**No.** 583  
**MAb ID** 36.1(ARP 329)  
**HXB2 Location** gp160 (361–381)  
**Author Location** gp120 (362–381 LAI)  
**Epitope** FKQSSGGDPEIVTHSFNCGGE  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 V4  
**References** Moore *et al.* 1994c; Thiriart *et al.* 1989  
 • 36.1: UK Medical Research Council AIDS reagent: ARP329.  
 • 36.1: The relative affinity for denatured/native gp120 is >30 – mutations 380 G/F, 381 E/P impair binding. Moore *et al.* [1994c]

**No.** 584  
**MAb ID** C12  
**HXB2 Location** gp160 (361–381)  
**Author Location** gp120 (362–381 LAI)  
**Epitope** FKQSSGGDPEIVTHSFNCGGE  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120 CD4i, gp120 V4  
**Research Contact** George Lewis  
**References** Dorfman *et al.* 2006; Choe *et al.* 2003; Moore *et al.* 1994d; Abacioglu *et al.* 1994; Moore *et al.* 1994c; Moore & Ho 1993  
**Keywords** antibody binding site definition and exposure, co-receptor

• C12: The CDR3 regions of CD4i Abs (E51, 412d, 17b, C12 and 47e) were cloned onto human IgG1 and tested for their ability to inhibit CCR5 binding. Only E51 successfully immunoprecipitated gp120. Dorfman *et al.* [2006] (**co-receptor**)  
 • C12: C12 was obtained from an HIV-1 infected individual with a potent and broadly neutralizing activity of his serum. It was shown that scFv C12 was sulfate-modified and it is implied that the sulfates are localized exclusively within the heavy chain CDR3 region of this MAb. Binding efficiency of scFv C12 to ADA gp120 was doubled in the presence of CD4, showing that this MAb is a CD4-induced. Association of scFv

C12 with ADA gp120-CD4-Ig complex was partially inhibited by a sulfated peptide with a sequence corresponding to the CCR5 amino terminus, indicating that C12 binds a CD4-enhanced epitope overlapping the binding domain of CCR5 amino terminus. scFv C12 was shown to efficiently bind to gp120 of three R5 isolates but not to the HXBc2 X4 isolate. Choe *et al.* [2003] (**antibody binding site definition and exposure, co-receptor**)  
 • C12: C3 region – epitope boundaries mapped by peptide scanning, core FNCGG. Abacioglu *et al.* [1994]  
 • C12: The relative affinity for denatured/native gp120 is >30 – mutations 380 G/F, 381 E/P, and 384 Y/E impair binding – also binds GEFFYCNSTQLFNS, gp120(380-393 LAI) Moore *et al.* [1994c]  
 • C12: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

**No.** 585  
**MAb ID** 2F19C  
**HXB2 Location** gp160 (363–365)  
**Author Location** gp120 (HIV2ROD)  
**Epitope** APGK  
**Subtype** HIV-2  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* HIV-2 ROD  
**Species (Isotype)** mouse  
**Ab Type** gp120 C3  
**References** Matsushita *et al.* 1995  
 • 2F19C: Binds in WB, but binds poorly to Env on the cell surface, APGK is the core binding region. Matsushita *et al.* [1995]

**No.** 586  
**MAb ID** 110.D  
**HXB2 Location** gp160 (380–393)  
**Author Location** gp120 (380–393 LAI)  
**Epitope** GEFFYCNSTQLFNS  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C3  
**Research Contact** F. Traincard, Pasteur Institute, France  
**References** Valenzuela *et al.* 1998; Moore *et al.* 1994c  
 • 110.D: The relative affinity for denatured/native gp120 is >50. Moore *et al.* [1994c]

**No.** 587  
**MAb ID** B32  
**HXB2 Location** gp160 (380–393)  
**Author Location** gp120 (380–393 LAI)  
**Epitope** GEFFYCNSTQLFNS  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C3

**References** Abacioglu *et al.* 1994; Moore *et al.* 1994c

- B32: C3 region – epitope boundaries mapped by peptide scanning – FFY(core) Abacioglu *et al.* [1994]
- B32: The relative affinity for denatured/native gp120 is >100 – mutations 380 G/F, 381 G/P, 382 F/L, 384 Y/E, and 386 N/R impair binding. Moore *et al.* [1994c]

**No.** 588

**MAb ID** polyclonal (VEI4)

**HXB2 Location** gp160 (391–413)

**Author Location** Env

**Epitope** FNSTWFNSTWSTEGSNNTGSDT

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 V4

**References** Carlos *et al.* 1999

- Antibody response to the epitopes in a vaccine construct (VEI) containing peptides from 5 hypervariable regions of gp120 was detected in the sera of HIV-1 positive subjects, including sera from 6 non-subtype B infections – serum samples from San Francisco, Canada and Puerto Rico cohort showed presence of antibodies against all five VEI hypervariable regions, but most consistently against the V3 region peptide NNNTRKSIRIGPGRAFYTGGDIGNIRQ. Carlos *et al.* [1999]

**No.** 589

**MAb ID** B15

**HXB2 Location** gp160 (395–400)

**Author Location** gp120 (395–400 BH10)

**Epitope** WFNSTW

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG2b)

**Ab Type** gp120 V4

**Research Contact** George Lewis

**References** Abacioglu *et al.* 1994; Moore *et al.* 1993b; Moore & Ho 1993

- B15: V4 region – epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]
- B15: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]
- B15: Binds native BH10 gp120 with 5 fold less affinity than denatured – does not bind native or denatured MN gp120. Moore *et al.* [1993b]

**No.** 590

**MAb ID** B34

**HXB2 Location** gp160 (395–400)

**Author Location** gp120 (395–400 BH10)

**Epitope** WFNSTW

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG2b)

**Ab Type** gp120 V4

**References** Abacioglu *et al.* 1994

- B34: V4 region – epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

**No.** 591

**MAb ID** 7F11

**HXB2 Location** gp160 (397–439)

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:*  
gp120

**Species (Isotype)** mouse

**References** Nilsen *et al.* 1996; Lasky *et al.* 1987

- 7F11: There is another MAb with this name that binds to integrase. Nilsen *et al.* [1996]

**No.** 592

**MAb ID** E51

**HXB2 Location** gp160 (420–423)

**Author Location** gp120 (420–423 HXB2)

**Epitope** IKQI

**Subtype** B

**Neutralizing** P

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CD4i, gp120 CCR5B5

**Research Contact** Joseph

Sodroski,

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**References** Kothe *et al.* 2007; Dorfman *et al.* 2006; Haynes *et al.* 2005; Choe *et al.* 2003; Xiang *et al.* 2003

**Keywords**

antibody binding site definition and exposure, antibody generation, co-receptor, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- E51: Four consensus B Env constructs: full length gp160, un-cleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective un-cleaved version mediated infection using the CCR5 co-receptor. CD4 inducible MAbs 17b and E51 were tested for the ability to neutralize the various forms of Con B; as anticipated gp160 and gp145 were not neutralized by these two MAbs, but the gp160-201N/S mutant was neutralized with IC50 values of 10 ug/ml, suggesting increased formation and/or exposure of the co-receptor binding site. The poorly infectious clone WITO4160.27 was also somewhat susceptible to neutralization by these clones. Kothe *et al.* [2007] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)
- E51: The CDR3 regions of CD4i Abs (E51, 412d, 17b, C12 and 47e) were cloned onto human IgG1 and tested for their ability to inhibit CCR5 binding. Only E51 successfully immunoprecipitated gp120. The sulfated peptide from E51 (pE51) efficiently bound gp120, was enhanced by CD4, and could neutralize HIV-1 more effectively than peptides based



on CCR5. pE51 was able to block infection by a range of subtype B isolates. Dorfman *et al.* [2006] (**co-receptor**)

- E51: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. E51 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)
- E51: E51 was obtained from an HIV-1 infected individual with a potent ELISA response to the gp120. It was shown that this MAb could be sulfate-modified. The results indicated that the sulfates present on E51 are localized on tyrosines within its heavy chain CDR3 region and that they contribute to E51's ability to associate with gp120 of the ADA isolate. Binding efficiency of E51 to ADA gp120 was increased by 25% in the presence of CD4, showing that E51 is a CD4i Ab. Association of E51 with ADA gp120-CD4-Ig complex was inhibited by a sulfated peptide with a sequence corresponding to the CCR5 amino terminus, indicating that E51 binds a CD4-enhanced epitope overlapping the binding domain of CCR5 amino terminus. Neutralization assays showed that E51 neutralizes primary R5 and R5X4 isolates more efficiently, and X4 isolates less efficiently, than CD4i Abs 17b and 48d. scFv E51 was shown to efficiently bind to gp120 of three R5 isolates and to the HXBc2 X4 isolate. Choe *et al.* [2003] (**antibody binding site definition and exposure, co-receptor, neutralization**)
- E51: E51 recognizes a highly conserved epitope localized in the basic  $\beta$ 19-strand (gp120 aa420-423), a region involved in CCR5 binding. The MAb was isolated from an EBV transformed B-cell line established from an HIV+ individual undergoing early STI. Fab fragments were also produced. E51, like CD4i MAb 17b, blocks CCR5 binding to sCD4-bound gp120. The presence of sCD4 induces a conformational change in gp120, which enhances ligand recognition. The substitutions E381R, F383S, R419D I420R, K421D, Q422L, I423S, and Y435S (HXB2 numbering) all severely reduce 17b and E51 binding. All but I423S also diminish CCR5 binding by more than 50%. The mutation F383S also inhibits sCD4 binding and CD4BS MAb F105 binding, and K421D inhibits F105 binding, but not sCD4. E51 has more cross-neutralizing potency than other prototype CD4i MAbs (17b) for B and C clade isolates. E51 and 17b both neutralized HIV-1 clade B strains HXBc2 and ADA, while JR-FL and 89.6 were only neutralized by E51, not 17b. Clade C strains MCGP1.3 and SA32 were both inhibited by 17b and E51, but E51 was more potent against SA32. Xiang *et al.* [2003] (**antibody binding site definition and exposure, antibody generation, co-receptor, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 593

**MAb ID** JL413

**HXB2 Location** gp160 (421-436)

**Author Location** gp160 (421-436)

**Epitope** KQIINMWQEVGKAMYA

**Subtype** B

**Neutralizing** P

**Immunogen** autoimmune disease

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Karle *et al.* 2004

**Keywords** antibody generation, antibody sequence variable domain, co-receptor, subtype comparisons

- JL413: Phage display was used to create a library of gp120-binding single-chain fragments containing V domain (scFv) constructs derived from PBMC of lupus patients. Lupus patients rarely get HIV/AIDS and can make antibodies that bind to a conserved gp120 determinant. The scFv clone JL413 was able to induce dose-dependent, cross-clade neutralization of primary HIV-1 isolates ZA009 (R5, clade C); BR004 (R5, clade C); Ug046 (X4, clade D); SF162 (R5, clade B), and 231135 (clade B). The scFv clone JL413 recognizes a linear region that overlaps the CD4 T-cell binding site, in contrast to HIV-induced MAbs that bind to this region and are conformation dependent. Karle *et al.* [2004] (**antibody generation, co-receptor, subtype comparisons, antibody sequence variable domain**)

No. 594

**MAb ID** 5C2E5

**HXB2 Location** gp160 (422-431)

**Author Location** gp120 (406-415 IIIB)

**Epitope** QFINMWQEVK

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* gp120

**Species (Isotype)** mouse

**Ab Type** gp120 C4

**Research Contact** T. Gregory and R. Ward, Genentech, San Francisco

**References** Cordell *et al.* 1991; Lasky *et al.* 1987

- 5C2E5: Cross-competition with MAbs 5C2E5, ICR38.8f and ICR38.1a. Cordell *et al.* [1991]
- 5C2E5: Blocks the gp120-CD4 interaction. Lasky *et al.* [1987]

No. 595

**MAb ID** G3-211 (211/C)

**HXB2 Location** gp160 (423-437)

**Author Location** gp120 (423-437 IIIB)

**Epitope** IINMWQKVGKAMYAP

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* virus derived protein *Strain:* B clade IIIB *HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C4

**References** Pantophlet *et al.* 2004; Sun *et al.* 1989

**Keywords** vaccine antigen design

- G3-211: Note – it is not clear if 211/C and G3-211 are the same antibodies. By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only

three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 211/C Pantophlet *et al.* [2004] (**vaccine antigen design**)

- G3-211: G3-211, 42, 299, 508, 519, 536, 537: Cross-react with diverse strains by immunofluorescence – blocks HIV binding to CD4+ cells – different neutralization efficiencies. Sun *et al.* [1989]

**No.** 596

**MAb ID** G3-537

**HXB2 Location** gp160 (423–437)

**Author Location** gp120 (423–437 IIIB)

**Epitope** IINMWQKVGKAMYAP

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* virus derived protein *Strain:* B clade IIIB *HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C4

**References** Zwick *et al.* 2003; McKeating *et al.* 1992b; Ho *et al.* 1991b; Sun *et al.* 1989

**Keywords** antibody interactions

- G3-537: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the C4 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- G3-537: Weakly neutralizing – binds to a linear binding domain of gp120, NMWQEVGKAMYAPPISG. McKeating *et al.* [1992b]
- G3-537, 211, 299, 508, 519, 536, 42: Cross-react with diverse strains by immunofluorescence – blocks HIV binding to CD4+ cells – different neutralization efficiencies. Sun *et al.* [1989]

**No.** 597

**MAb ID** polyclonal

**HXB2 Location** gp160 (425–436)

**Author Location** gp120

**Epitope** NMWQEVGKAMYA

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB *Adjuvant:* Cholera toxin (CT)

**Species (Isotype)** mouse (IgA)

**Ab Type** gp120 CD4BS

**References** Bukawa *et al.* 1995

- Polyclonal secretory IgA antibody raised by mucosal immunization is able to neutralize IIIB, SF2, and MN – HIV-1 neutralization may be due to the V3, CD4 or HPG30 component of the multicomponent peptide immunogen. Bukawa *et al.* [1995]

**No.** 598

**MAb ID** 1795

**HXB2 Location** gp160 (425–441)

**Author Location** gp120 (425–441 IIIB)

**Epitope** NMWQEVGKAMYAPPISG

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* poliovirus *HIV component:* Env

**Species (Isotype)**

**Ab Type** gp120 CD4BS

**References** McKeating *et al.* 1992b

- 1795: CD4 binding site – weakly neutralizing – binding inhibited by WQEVGKAMYA, GKAM may be involved. McKeating *et al.* [1992b]

**No.** 599

**MAb ID** ICR38.1a (38.1a, 388/389, ARP388/389)

**HXB2 Location** gp160 (429–438)

**Author Location** gp120 (427–436 BRU)

**Epitope** EVGKAMYAPP

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BH10 *HIV component:* gp120

**Species (Isotype)** rat (IgG2b)

**Ab Type** gp120 C3, gp120 C4

**References** Holl *et al.* 2006a; Vella *et al.* 2002; Kropelin *et al.* 1998; Peet *et al.* 1998; Jeffs *et al.* 1996; Moore *et al.* 1993b; McKeating *et al.* 1993a; McKeating *et al.* 1993b; McKeating *et al.* 1992c; McKeating *et al.* 1992a; McKeating *et al.* 1992b; Cordell *et al.* 1991

**Keywords** dendritic cells, neutralization

- ICR38.1a: UK Medical Research Council AIDS reagent: ARP388/ARP389.
- ICR38: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- ICR38.1a: Called ARP388/ARP389: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs – lists epitope as WQEVGKAMYA. Vella *et al.* [2002]
- ICR38.1a: Called 388/389 – anti-C1 region MAb 87-135/9 blocks gp120 interaction with CD4+ cells – blocking activity is additive when combined with antibodies which bind in the C4 region of gp120 (F105, 388/389, and b12) Kropelin *et al.* [1998]
- ICR38.1a: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – ICR38.1a was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

- ICR38.1a: Called 38.1a – 10 to 20 fold increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996]
- ICR38.1a: Studied in the context of a neutralization escape mutant. McKeating *et al.* [1993a]
- ICR38.1a: Unreactive with solid-phase decapeptide, competed in solution phase assay – ICR 38.1a and ICR 38.8f were initially reported to be independent MABs, but are actually subclones of the same MAB. Moore *et al.* [1993b]
- ICR38.1a: Weakly neutralizing – binds linear determinant in the CD4 binding domain – cross-competition with MABs G3-536, 5C2E5, and ICR38.8f. Cordell *et al.* [1991]; McKeating *et al.* [1992b]
- ICR38.1a: Unable to exert a synergistic effect in combination with V3 directed MABs, in contrast to MAB 39.13g, that binds to a conformational epitope involved in CD4 binding. McKeating *et al.* [1992a]

No. 600

**MAB ID** G3-299

**HXB2 Location** gp160 (429–438)

**Author Location** gp120 (429–438 BRU)

**Epitope** EVGKAMYAPP

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* virus derived protein *HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C4

**Research Contact** M. Fung and Tanox Biosystems Inc and David Ho, ADARC, NY

**References** Zwick *et al.* 2003; Kwong *et al.* 2002; Parren *et al.* 1998a; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Binley *et al.* 1997a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Moore *et al.* 1993b; Sun *et al.* 1989

**Keywords** antibody binding site definition and exposure, antibody interactions

- G3-299: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MABs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MABs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MABs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the C4-V3 MABs used. Zwick *et al.* [2003] (**antibody interactions**)
- G3-299: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAB ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MABs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of

binding to the gp120 monomer, except the potent CD4BS neutralizing MAB b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MABs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MABs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the G3-299 epitope as V3 loop/outer domain. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

- G3-299: The MAB and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-299: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997]
- G3-299: Discontinuous V3-C4 epitope, binding enhanced by a few anti-C1, anti-CD4 binding site, and V2 MABs – binding reciprocally inhibited by anti-V3 MABs – G3-229 enhances the binding of some anti-V2 MABs. Moore & Sodroski [1996]
- G3-299: Epitope described as KQIINMWQKVGKAMYAPPIS – binding resulted in slight gp120 dissociation from virus and exposure of the gp41 epitope for MAB 50-69. Poignard *et al.* [1996a]
- G3-299: Binds with higher affinity to monomer than to oligomer, slow association rate, although faster than other C4 MABs tested, with more potent neutralization of lab strain. Sattentau & Moore [1995]
- G3-299: C4 region – binds HXB2 20mer KQIINMWQKVGKAMYAPPIS, and SF-2 and MN gp120s – G3-42, G3-299 lower affinity than G3-508, G3-519, and G3-536 – bound native gp120, not denatured – poor peptide binding, epitope spans V3-C4 regions – 433A/L, 435Y/H and 430V/S substitutions impaired binding, V3 loop cleavage or insertion abolished binding. Moore *et al.* [1993b]
- G3-299: Best neutralization of IIIB in panel of 7 MABs that bind overlapping epitope. Sun *et al.* [1989]

No. 601

**MAB ID** G3-42 (G3 42)

**HXB2 Location** gp160 (429–438)

**Author Location** gp120 (429–438 BRU)

**Epitope** EVGKAMYAPP

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* virus derived protein *Strain:* B clade IIIB *HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C4

**Research Contact** Tanox Biosystems Inc and David Ho, ADARC, NY, NY

**References** Koefoed *et al.* 2005; Zwick *et al.* 2003; Jagodzinski & Trzeciak 2000; Binley *et al.* 1999; Binley *et al.* 1997a; Trkola *et al.* 1996a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Jagodzinski *et al.* 1996; Sattentau & Moore 1995; Thali *et al.* 1993; Moore *et al.* 1993b; Sun *et al.* 1989

**Keywords** antibody binding site definition and exposure, antibody interactions

- G3-42: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. G3-42 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a linear C4/V3 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- G3-42: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the C4-V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 0.5beta: MAbs 0.5beta and G3-42 were used to study synthesis of oligomeric and monomeric forms of Env – inhibition of glycosylation by tunicamycin results in reduction of oligomeric gp120 at the cell surface and of monomer in the cytoplasm – neither MAb recognized non-glycosylated Env precursor. Jagodzinski & Trzeciak [2000]
- G3-42: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAb IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]
- G3-42: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – CRDS potentially inhibits G3-42 binding – G3-42 epitope described as KVGKAMYAPP. Jagodzinski *et al.* [1996]
- G3-42: Inhibits binding of many anti-V3, -CD4 binding site, and -C4 region MAbs – enhances binding of some anti-V2 region MAbs. Moore & Sodroski [1996]
- G3-42: Epitope described as KQIINMWQKVGKAMYAPPIS – binding resulted in slight gp120 dissociation from virus and exposure of the gp41 epitope for MAb 50-69. Poignard *et al.* [1996a]
- G3-42: Called G3 42 – Does not inhibit gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study – described as V3-C4 discontinuous epitope. Trkola *et al.* [1996a]
- G3-42: Binds with higher affinity to monomer than to oligomer, slow association rate. Sattentau & Moore [1995]
- G3-42: C4 region – binds HXB2 20mer KQIINMWQKVGKAMYAPPIS, and SF-2 and MN gp120s – G3-42, G3-299 have lower affinity than G3-508, G3-519, and G3-536 – bound native gp120, not denatured – poor peptide binding, epitope spans V3-C4 regions – 433A/L, 435Y/H and 430V/S substitutions impaired binding, V3 loop insertion abolished binding. Moore *et al.* [1993b]
- G3-42: Inhibits binding of CD4 inducible MAb 48d. Thali *et al.* [1993]
- G3-42: Neutralization of IIIB but not RF. Sun *et al.* [1989]

**No.** 602

**MAb ID** G3-508 (G3 508)

**HXB2 Location** gp160 (429–438)

**Author Location** gp120 (429–438 BRU)

**Epitope** EVGKAMYAPP

**Neutralizing L**

**Immunogen** vaccine

*Vector/Type:* virus derived protein *Strain:*

B clade IIIB *HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C4

**Research Contact** M. Fung and Tanox Biosystems Inc and David Ho, ADARC, NY

**References** Binley *et al.* 1998; Parren *et al.* 1998a; Binley *et al.* 1997a; Trkola *et al.* 1996a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Moore *et al.* 1993b; Thali *et al.* 1993; Sun *et al.* 1989

- G3-508: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- G3-508: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-508: Inhibits binding of some V3, C4 and CD4 binding site MAbs, enhances binding of V2 region MAbs. Moore & Sodroski [1996]
- G3-508: Binding resulted in slight gp120 dissociation from virus and exposure of the gp41 epitope for MAb 50-69. Poignard *et al.* [1996a]
- G3-508: Called G3 508 – inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- G3-508: Binds with higher affinity to monomer than to oligomer, slow association rate. Sattentau & Moore [1995]

- G3-508: C4 region – binds HXB2 20mer KQIIN-MWQKVGKAMYAPPIS, and SF-2 and MN gp120s – bound denatured with 10 fold greater affinity than native – 433A/L, 435Y/H and 430V/S substitutions impaired binding. Moore *et al.* [1993b]
- G3-508: Inhibits binding of CD4 inducible MAb 48d. Thali *et al.* [1993]
- G3-508: Neutralization of IIIB and RF. Sun *et al.* [1989]

**No.** 603

**Mab ID** G3-519

**HXB2 Location** gp160 (429–438)

**Author Location** gp120 (429–438 BRU)

**Epitope** EVGKAMYAPP

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* virus derived protein *Strain:*

B clade IIIB *HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C4

**Research Contact** Tanox Biosystems Inc and David Ho, ADARC, NY

**References** Zwick *et al.* 2003; Binley *et al.* 1999; Parren *et al.* 1998a; Wyatt *et al.* 1997; Binley *et al.* 1997a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; D'Souza *et al.* 1994; Moore *et al.* 1993b; Moore & Ho 1993; Sun *et al.* 1989

**Keywords** antibody interactions

- G3-519: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the C4 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- G3-519: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAb IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]

- G3-519: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-519: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997]
- G3-519: Non-reciprocal enhanced binding in the presence of the C5 MAb 1C1 and the C1 MAb 135/9 – reciprocal enhanced binding with some V2 MAbs. Inhibited binding the presence of some C4, V3 and CD4 binding site MAbs. Moore & Sodroski [1996]
- G3-519: Epitope described as KVGKAMYAPP – binding resulted in slight gp120 dissociation from virus but no significant exposure of the gp41 epitope for MAb 50-69. Poignard *et al.* [1996a]
- G3-519: Binds with higher affinity to monomer than to oligomer, slow association rate. Sattentau & Moore [1995]
- G3-519: Included in a multi-lab study for antibody characterization, and binding and neutralization assay comparison, also binds IIIB: IINMWQKVGKAMYAPP. D'Souza *et al.* [1994]
- G3-519: Neutralizes IIIB, is reactive with SF-2 gp120, mild inhibition of HIV-1 + sera binding to IIIB gp120. Moore & Ho [1993]
- G3-519: C4 region – binds HXB2 20mer KQIIN-MWQKVGKAMYAPPIS, and SF-2 and MN gp120s – bound denatured with 5 fold greater affinity than native – 433A/L, 435Y/H, 438P/R and 430V/S substitutions impaired binding. Moore *et al.* [1993b]
- G3-519: Best neutralization of RF in panel of 7 MAbs that bind overlapping epitope. Sun *et al.* [1989]

**No.** 604

**Mab ID** G3-536

**HXB2 Location** gp160 (429–438)

**Author Location** gp120 (429–438 BRU)

**Epitope** EVGKAMYAPP

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* virus derived protein *Strain:*

B clade IIIB *HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 C4

**Research Contact** Tanox Biosystems Inc and David Ho, ADARC, NY

**References** Parren *et al.* 1998a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Gorny *et al.* 1994; Moore *et al.* 1993b; Moore & Ho 1993; McKeating *et al.* 1992b; Cordell *et al.* 1991; Ho *et al.* 1991b; Sun *et al.* 1989

- G3-536: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- G3-536: Inhibits binding of some V3, C4 and CD4 binding site MAbs, enhances binding of V2 region MAbs. Moore & Sodroski [1996]

- G3-536: Epitope described as KVGKAMYAPP. Poignard *et al.* [1996a]
- G3-536: Binds with higher affinity to monomer than to oligomer, slow association rate. Sattentau & Moore [1995]
- G3-536: Enhances binding of anti-V2 MAb 697-D. Gorny *et al.* [1994]
- G3-536: Neutralizes IIIB, is reactive with SF-2 gp120, mild inhibition of HIV-1 + sera binding to IIIB gp120. Moore & Ho [1993]
- G3-536: C4 region – binds HXB2 20mer KQIIN-MWQKVGKAMYAPPIS, and SF-2 and MN gp120s – bound denatured with 15 fold greater affinity than native – 433A/L, 435Y/H, 438P/R, and 430V/S substitutions impaired binding. Moore *et al.* [1993b]
- G3-536: Weakly neutralizing – binds to a linear determinant in the CD4 binding domain of gp120. McKeating *et al.* [1992b]
- G3-536: Cross-competition with MAbs 5C2E5, ICR38.8f and ICR38.1a. Cordell *et al.* [1991]
- G3-536: Weak neutralization of IIIB and RF – cross-react with diverse strains by immunofluorescence – blocks HIV binding to CD4+ cells – epitope: IINMWQKVGKAMYAP. Sun *et al.* [1989]

No. 605

MAB ID ICR38.8f

HXB2 Location gp160 (429–438)

Author Location gp120 (429–438 BRU)

Epitope EVGKAMYAPP

Neutralizing L

Immunogen vaccine

Vector/Type: protein Strain: B clade BH10  
HIV component: gp120

Species (Isotype) rat (IgG2b)

Ab Type gp120 C4

References Moore *et al.* 1993b; Cordell *et al.* 1991

- ICR38.8f: ICR 38.1a and ICR 38.8f were initially reported to be independent MAbs, but are actually subclones of the same MAb. Moore *et al.* [1993b]
- ICR38.8f: Weakly neutralizing – binds linear determinant in the CD4 binding domain – cross-competition with ICR38.1a, 5C2E5, and G3-536. Cordell *et al.* [1991]

No. 606

MAB ID MO86/C3

HXB2 Location gp160 (429–443)

Author Location gp120 (429–443)

Epitope EVGKAMYAPPISGQI

Neutralizing

Immunogen in vitro stimulation or selection

Species (Isotype) human (IgM)

Ab Type gp120 C4

References Ohlin *et al.* 1992

- MO86: Generated in response to IIIB Env 286-467 upon *in vitro* stimulation of uninfected-donor lymphocytes. Ohlin *et al.* [1992]

No. 607

MAB ID 13H8

HXB2 Location gp160 (431–440)

Author Location gp120 (412–453)

Epitope GKAMYAPPIS

Neutralizing L

Immunogen vaccine

Vector/Type: protein Strain: B clade MN

Species (Isotype) mouse (IgG)

Ab Type gp120 C4

References Jeffs *et al.* 1996; Nakamura *et al.* 1993; Nakamura *et al.* 1992

- 13H8: Binds V3 and C4 peptides (J. P. Moore, per. comm.)
- 13H8: 3 and 4.5 fold increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120, respectively. Jeffs *et al.* [1996]
- 13H8: Bound diverse strains, neutralizing activity against MN. Nakamura *et al.* [1993]
- 13H8: Cross blocks 5C2 in IIIB-rsgp160 ELISA – reactive with diverse strains in rgp120 ELISA. Nakamura *et al.* [1992]

No. 608

MAB ID G45-60

HXB2 Location gp160 (431–440)

Author Location gp120 (429–438 BRU)

Epitope GKAMYAPPIS

Neutralizing L

Immunogen vaccine

Vector/Type: virus derived protein Strain: B clade IIIB HIV component: gp120

Species (Isotype) mouse (IgG1)

Ab Type gp120 C4

References Jagodzinski *et al.* 1996; Moore & Sodroski 1996; Gorny *et al.* 1994; Moore *et al.* 1993b; Sun *et al.* 1989

- G45-60: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus CRDS inhibits G45-60 binding. Jagodzinski *et al.* [1996]
- G45-60: Non-reciprocal enhancement of G45-60 binding by some C1 and C5 antibodies – reciprocal enhancement of some V2 region MAbs – reciprocal inhibition with many MAbs that bind to the V3, C4 and CD4 binding site regions. Moore & Sodroski [1996]
- G45-60: Enhances binding of anti-V2 MAb 697-D. Gorny *et al.* [1994]
- G45-60: C4 region – binds HXB2 20mer KQIIN-MWQKVGKAMYAPPI, decapeptide flanking peptides also bound – bound equivalently to native and denatured gp120 – 433A/L and 435Y/H (not 430V/S) substitutions impaired binding. Moore *et al.* [1993b]

No. 609

MAB ID polyclonal

HXB2 Location gp160 (432–451)

Author Location gp120 (42–61 LAI)

Epitope KAMYAPPISGQIRCSSNITG

Subtype B

Neutralizing no

Immunogen vaccine

Vector/Type: vaccinia HIV component: Env

Species (Isotype) mouse

Ab Type gp120 C4

References Collado *et al.* 2000

- Vaccinia p14 can elicit NAb and p39 tends to be immunodominant, so these two proteins were fused to regions of HIV-1 Env – reduced glycosylation was noted when p14 or p39 was placed in the N-term region of the fusion protein – chimeric proteins shifted the Env Ab response from V3 to either a C1 or C4 domain, depending on the construct – all chimeric Env proteins: 14kEnv, 39kEnv, and Env39k elicited a strong Ab response to the C1 region of gp120 (LFCAS-DAKAYDTEVHNVWAT), and Env39k mounted a strong response to the C4 region (KAMYAPPISGQIRCSSNITG) Colorado *et al.* [2000]

No. 610

**MAb ID** 1662

**HXB2 Location** gp160 (433–439)

**Author Location** gp120 (IIIB)

**Epitope** AMYAPPI

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *HIV component:* Env

**Species (Isotype)**

**Ab Type** gp120 C4

**References** McKeating *et al.* 1992b

- 1662: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 611

**MAb ID** 1663

**HXB2 Location** gp160 (433–439)

**Author Location** gp120 (IIIB)

**Epitope** AMYAPPI

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *HIV component:* Env

**Species (Isotype)**

**Ab Type** gp120 C4

**References** McKeating *et al.* 1992b

- 1663: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 612

**MAb ID** 1664

**HXB2 Location** gp160 (433–439)

**Author Location** gp120 (IIIB)

**Epitope** AMYAPPI

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *HIV component:* Env

**Species (Isotype)**

**Ab Type** gp120 C4

**References** McKeating *et al.* 1992b

- 1664: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 613

**MAb ID** 1697

**HXB2 Location** gp160 (433–439)

**Author Location** gp120 (IIIB)

**Epitope** AMYAPPI

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *HIV component:* Env

**Species (Isotype)**

**Ab Type** gp120 C4

**References** McKeating *et al.* 1992b

- 1697: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 614

**MAb ID** 1794

**HXB2 Location** gp160 (433–442)

**Author Location** gp120 (IIIB)

**Epitope** AMYAPPISGQ

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *HIV component:* Env

**Species (Isotype)**

**Ab Type** gp120 C4

**References** McKeating *et al.* 1992b

- 1794: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 615

**MAb ID** 1804

**HXB2 Location** gp160 (433–442)

**Author Location** gp120 (IIIB)

**Epitope** AMYAPPISGQ

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *HIV component:* Env

**Species (Isotype)**

**Ab Type** gp120 C4

**References** McKeating *et al.* 1992b

- 1804: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 616

**MAb ID** 1807

**HXB2 Location** gp160 (433–442)

**Author Location** gp120 (IIIB)

**Epitope** AMYAPPISGQ

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *HIV component:* Env

**Species (Isotype)**

**Ab Type** gp120 C4

**References** McKeating *et al.* 1992b

- 1807: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

No. 617

**MAb ID** 1808

**HXB2 Location** gp160 (433–442)

**Author Location** gp120 (IIIB)**Epitope** AMYAPPISGQ**Neutralizing** no**Immunogen** vaccine*Vector/Type:* poliovirus *HIV component:* Env**Species (Isotype)****Ab Type** gp120 C4**References** McKeating *et al.* 1992b

- 1808: Did not bind to native gp120, epitope not exposed. McKeating *et al.* [1992b]

**No.** 618**MAb ID** polyclonal (VEI5)**HXB2 Location** gp160 (454–474)**Author Location** Env**Epitope** LTRDGGNNNESEIFRPGGGD**Neutralizing****Immunogen** HIV-1 infection**Species (Isotype)** human**Ab Type** gp120 V1, gp120 V2, gp120 V3, gp120 V4, gp120 V5**References** Carlos *et al.* 1999

- Antibody response to the epitopes in a vaccine construct (VEI) containing peptides from 5 hypervariable regions of gp120 was detected in the sera of HIV-1 positive subjects, including sera from 6 non-subtype B infections – serum samples from San Francisco, Canada and Puerto Rico cohort showed presence of antibodies against all five VEI hypervariable regions, but most consistently against the V3 region peptide NNNTRKSIRIGPGRAFYYTTGDIGNIRQ. Carlos *et al.* [1999]

**No.** 619**MAb ID** polyclonal**HXB2 Location** gp160 (460–467)**Author Location** gp120 (LAI)**Epitope** NNNNGSEI**Subtype** B**Neutralizing****Immunogen** HIV-1 infection, vaccine*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160**Species (Isotype)** human**Ab Type** gp120 V5**References** Loomis-Price *et al.* 1997

- HIV-1 + positive individuals were given a gp160 vaccine as immunotherapy, and this region was the most reactive new epitope as measured by a modified Pepsan technique which improved sensitivity – 4/14 showed vaccine-induced reactivity. Loomis-Price *et al.* [1997]

**No.** 620**MAb ID** CRA1 (CRA-1, CRA1(ARP 323))**HXB2 Location** gp160 (461–470)**Author Location** gp120 (451–470 LAI)**Epitope** SNNSESEIFRL**Subtype** B**Neutralizing** no**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade LAI*HIV component:* Env**Species (Isotype)** mouse (IgG)**Ab Type** gp120 V5-C5**Research Contact** M. Page, NIBSC, UK**References** Koefoed *et al.* 2005; Yang *et al.* 2000; Trkola *et al.* 1996a; Moore & Sodroski 1996; Moore *et al.* 1994c; Moore *et al.* 1994d; Moore & Ho 1993**Keywords** antibody binding site definition and exposure

- CRA1: UK Medical Research Council AIDS reagent: ARP323.
- CRA1: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. CRA1 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MABs, representing a MAb with a linear C5 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- CRA1: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MABs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MABs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MABs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- CRA1: C5 region linear epitope, binds weakly to nondenatured monomeric gp120 – reciprocal binding inhibition with anti-C5 antibodies IC1 and M91 – non-reciprocal binding enhancement some C1 and V2 antibodies – non-reciprocal binding inhibition of some CD4 binding site antibodies. Moore & Sodroski [1996]
- CRA1: Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- CRA1: Some C5 mutations abrogate binding 470 P/L or G, 475 M/S, some C2 mutations enhance binding. Moore *et al.* [1994d]
- CRA1: The relative affinity for denatured/native gp120 is 24 – C5 mutations 470 P/L or G, 475 M/S impairs binding to the native gp120 – only mutation 470 P/L impairs binding to denatured. Moore *et al.* [1994c]
- CRA1: Bound preferentially to denatured IIIB and SF2 gp120. Moore & Ho [1993]

**No.** 621**MAb ID** M91**HXB2 Location** gp160 (461–470)**Author Location** gp120 (451–470 LAI)**Epitope** SNNSESEIFRL**Subtype** B**Neutralizing** no**Immunogen** vaccine*Vector/Type:* protein *HIV component:* Env**Species (Isotype)** rat (IgG2a)



- Ab Type** gp120 V5-C5  
**Research Contact** Fulvia di Marzo Veronese  
**References** Zwick *et al.* 2003; Yang *et al.* 2000; Binley *et al.* 1998; Ditzel *et al.* 1997; Moore & Sodroski 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; di Marzo Veronese *et al.* 1992  
**Keywords** antibody interactions
- M91: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C5-binding MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
  - M91: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
  - M91: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
  - M91: C5 region linear epitope, binds weakly to nondenatured monomeric gp120 – M91 binding was enhanced by 1C1, but 1C1 binding was inhibited by M91 – non-reciprocal binding enhancement of C1 and V2 antibodies – non-reciprocal binding inhibition of CD4 binding site antibodies. Moore & Sodroski [1996]
  - M91: The relative affinity for denatured/native gp120 is 24 – mutation in position 470 P/L impairs binding. Moore *et al.* [1994c]
  - M91: 470 P/L impairs binding, but not 475 D/V, in contrast to CRA1 – some C2 mutations can enhance binding. Moore *et al.* [1994d]
  - M91: Immunoblot reactive, RIP negative, but precipitates deglycosylated gp120 – reacts with strains IIIB, 451, MN, RF, and RUTZ. di Marzo Veronese *et al.* [1992]

No. 622

Mab ID 9201

HXB2 Location gp160 (471–482)

Author Location gp120 (475–486 LAI)

Epitope GGGDMRDNRWSE

Subtype B

Neutralizing no

Immunogen vaccine

Vector/Type: peptide

Species (Isotype) mouse (IgG1)

Ab Type gp120 C5

Research Contact Du Pont de Nemours, Boston, MA

References Dairou *et al.* 2004; McDougal *et al.* 1996

Keywords antibody binding site definition and exposure

- 9201: This paper describes a slightly different epitope, stating 9201 was raised against the peptide MRDNWRSELIKY, located within the alpha 5 helix in the C5 terminal region of gp120. Two MAbs were used to determine the photodamage location in HIV-1 Env induced by sulfonated anionic porphyrins. The negatively charged porphyrins interact with positive charge in the V3 loop. When light activated, they damage amino acid side chains in the C5 region of Env, as evidenced by inhibition of binding of C5 MAb 9201, but not V3 MAb 13105100. Anionic porphyrins could be used in targeted photodynamic decontamination of biological fluids, such as blood, killing HIV without disabling the function of desirable transfusion products. Dairou *et al.* [2004] (**antibody binding site definition and exposure**)
- 9201: Does not neutralize LAI. This paper notes the peptide binding region is GGGDMRDNRWSE. McDougal *et al.* [1996] (**antibody binding site definition and exposure**)

No. 623

Mab ID 1C1

HXB2 Location gp160 (471–490)

Author Location gp120 (471–490 LAI)

Epitope GGGDMRDNRSELYKYKVVK

Subtype B

Neutralizing

Immunogen vaccine

Vector/Type: protein Strain: B clade LAI

HIV component: Env

Species (Isotype) mouse (IgG)

Ab Type gp120 C5

Research Contact Repligen Inc, Cambridge, MA, commercial

References Zwick *et al.* 2003; Moore & Sodroski 1996;VanCott *et al.* 1995; Moore *et al.* 1994d;Moore *et al.* 1994c

Keywords antibody interactions

- 1C1: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C5-binding MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- 1C1: C5 region linear epitope, binds weakly to nondenatured monomeric gp120 – M91 binding was enhanced by 1C1, but 1C1 binding was inhibited by M91 – non-reciprocal binding enhancement of some C1 and V2 antibodies – non-reciprocal binding inhibition of some CD4 binding site antibodies. Moore & Sodroski [1996]
- 1C1: Linear epitope not exposed on conformationally intact gp120. VanCott *et al.* [1995]
- 1C1: The relative affinity for denatured/native gp120 is 15. Moore *et al.* [1994c]

- 1C1: C2 and V3 regions substitutions can influence binding. Moore *et al.* [1994d]

**No.** 624  
**MAb ID** 3F5  
**HXB2 Location** gp160 (471–490)  
**Author Location** gp120 (471–490 LAI)  
**Epitope** GGGDMRDNRSELYKYKVVK  
**Subtype** B  
**Neutralizing Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C5  
**Research Contact** S. Nigida, NCI, USA  
**References** Moore *et al.* 1994c  
 • 3F5: The relative affinity for denatured/native gp120 is 100. Moore *et al.* [1994c]

**No.** 625  
**MAb ID** 5F4/1  
**HXB2 Location** gp160 (471–490)  
**Author Location** gp120 (471–490 LAI)  
**Epitope** GGGDMRDNRSELYKYKVVK  
**Subtype** B  
**Neutralizing Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* HIV-2 ROD  
**Species (Isotype)** mouse  
**Ab Type** gp120 C5  
**Research Contact** S. Ranjbar, NIBSC, UK  
**References** Moore *et al.* 1994c  
 • 5F4/1: V5-C5 region – preferentially binds SDS-DTT denatured gp120 (>10 fold) – mutation 485 K/V impairs binding. Moore *et al.* [1994c]

**No.** 626  
**MAb ID** 660-178  
**HXB2 Location** gp160 (471–490)  
**Author Location** gp120 (471–490 LAI)  
**Epitope** GGGDMRDNRSELYKYKVVK  
**Subtype** B  
**Neutralizing Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C5  
**Research Contact** G. Robey, Abbott Labs  
**References** Moore *et al.* 1994d; Moore *et al.* 1994c  
 • 660-178: The relative affinity for denatured/native gp120 is >100. Moore *et al.* [1994c]  
 • 660-178: DeltaV1/V2 and DeltaV1/V2/V3 reduce binding – C2 and C5 mutations enhance binding. Moore *et al.* [1994d]

**No.** 627  
**MAb ID** 9301  
**HXB2 Location** gp160 (471–490)  
**Author Location** gp120 (471–490 LAI)  
**Epitope** GGGDMRDNRSELYKYKVVK

**Subtype B Neutralizing Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* Env

**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C5  
**Research Contact** Dupont, commercial  
**References** Wagner *et al.* 1996; Moore *et al.* 1994d; Moore *et al.* 1994c; Moore & Ho 1993; Skinner *et al.* 1988b  
 • 9301: Wagner *et al.* claim that Nea 9301 is anti-V3 – might they have meant MAb 9305? Wagner *et al.* [1996]  
 • 9301: The relative affinity for denatured/native gp120 is 19. Moore *et al.* [1994d]  
 • 9301: Bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

**No.** 628  
**MAb ID** B221 (221)  
**HXB2 Location** gp160 (471–490)  
**Author Location** gp120 (471–490 LAI)  
**Epitope** GGGDMRDNRSELYKYKVVK  
**Subtype** B  
**Neutralizing Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* gp160  
**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** gp120 C5  
**Research Contact** Rod Daniels  
**References** Billington *et al.* 2007; Holl *et al.* 2006a; Moore *et al.* 1994d; Moore *et al.* 1994c; Bristow *et al.* 1994; Moore & Ho 1993  
**Keywords** dendritic cells, neutralization

- B221: UK Medical Research Council AIDS reagent: ARP301.
- B221: Called 221. The MAb CA13 binds to the conserved C1 epitope EDIISLW and was used in conjunction with MAb 221, a MAb that binds to the gp120 C-terminal end, to explore the composition and stability of a highly stable trimeric rgp140 derived from a HIV-1 subtype D isolate containing intermonomer V3-derived disulfide bonds and lacking gp120/gp41 proteolytic processing. The stability of the trimer indicates it may be a good candidate for structural studies. Billington *et al.* [2007]
- 221: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- B221: MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp160 IIIB:NL43, MicroGenSys. Bristow *et al.* [1994]
- B221: The relative affinity for denatured/native gp120 is 12 – mutation 477 D/V impairs binding. Moore *et al.* [1994c]
- B221: Called 221 – C2 and V3 substitutions influence binding. Moore *et al.* [1994d]

- B221: Called 221 – bound preferentially to denatured IIIB gp120. Moore & Ho [1993]

**No.** 629  
**MAb ID** 8C6/1  
**HXB2 Location** gp160 (471–490)  
**Author Location** gp120 (471–490 LAI)  
**Epitope** GGGMDRDNWRSELYKYKVVVK  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 V5-C5  
**Research Contact** S. Ranjbar, NIBSC, UK  
**References** Moore *et al.* 1994c  
 • 8C6/1: UK Medical Research Council AIDS reagent: ARP3052.  
 • 8C6/1: V5-C5 region – preferentially binds SDS-DTT denatured gp120 (>30 fold) – mutation 485 K/V impairs binding. Moore *et al.* [1994c]

**No.** 630  
**MAb ID** H11  
**HXB2 Location** gp160 (472–477)  
**Author Location** gp120 (472–477 HXB2)  
**Epitope** GGDMRD  
**Subtype** B  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** mouse  
**Ab Type** gp120 C5  
**References** Pincus *et al.* 1996; Pincus & McClure 1993  
 • H11: Binds to gp120 but not to infected cells – when linked to ricin A, the immunotoxin did not mediate cell killing – sCD4 has no effect. Pincus & McClure [1993]; Pincus *et al.* [1996]

**No.** 631  
**MAb ID** W2  
**HXB2 Location** gp160 (472–491)  
**Author Location** gp120 (472–491 LAI)  
**Epitope** GGGMDRDNWRSELYKYKVVVKI  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Strain:* B clade LAI *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 C5  
**Research Contact** D. Weiner, U. Penn., USA  
**References** Moore *et al.* 1994c  
 • W2: The relative affinity for denatured/native gp120 is 30 – mutation 485 K/V impairs binding. Moore *et al.* [1994c]

**No.** 632  
**MAb ID** M38  
**HXB2 Location** gp160 (485–504)  
**Author Location** gp120 (490–508)  
**Epitope** KYKVVKEIPLGVAPTAKARR  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* virus *Strain:* B clade IIIB  
*HIV component:* HIV-1

**Species (Isotype)** mouse  
**Ab Type** gp120 C5  
**References** Maksiutov *et al.* 2002; Beretta & Dalgleish 1994; DeSantis *et al.* 1994; Lopalco *et al.* 1993; Grassi *et al.* 1991; Beretta *et al.* 1987  
 • M38: This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVP-TKADKRRSV, as well as to a fragment of IFN-related IFRD2 (PC4-B) protein, ARTKARSVRDKRA. Maksiutov *et al.* [2002]  
 • M38: Infected individuals have HLA class I-gp120 cross-reactive antibodies. DeSantis *et al.* [1994]  
 • M38: Binds to the carboxy terminus of gp120, in a gp41 binding region, and also to denatured human HLAs (antigenic homology) Lopalco *et al.* [1993]  
 • M38: Binds to gp120 and to a 80 kd human protein expressed on a small fraction of mononuclear cells in the lymph nodes. Beretta *et al.* [1987]

**No.** 633  
**MAb ID** Chim 1 (C-1)  
**HXB2 Location** gp160 (487–493)  
**Author Location** gp120 (492–498 HXB2)  
**Epitope** KVVKEIP?  
**Subtype** B  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** humanized chimpanzee  
**References** Pincus *et al.* 1996; Pincus & McClure 1993  
 • Chim 1: Binds to gp120 but not to infected cells – when linked to ricin A, the immunotoxin did not mediate cell killing – sCD4 has no effect. Pincus & McClure [1993]; Pincus *et al.* [1996]

**No.** 634  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (490–511)  
**Author Location** gp120 (495–516 BRU)  
**Epitope** KIEPLGVAPTAKARRVVQREKR  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Maksiutov *et al.* 2002; Hernandez *et al.* 2000  
 • This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVPTKADKRRSV, as well as to a fragment of IFN-related IFRD2 (PC4-B) protein, ARTKARSVRDKRA. Maksiutov *et al.* [2002]  
 • Chimeric peptide combining two peptides gp160(495-516 and 584-612) served as a specific and broadly reactive antigen for diagnostic detection of HIV-1. Hernandez *et al.* [2000]

**No.** 635  
**MAb ID** 110.1  
**HXB2 Location** gp160 (491–500)  
**Author Location** gp120 (491–500 LAI)  
**Epitope** IEPLGVAPT  
**Subtype** B  
**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* HIV infected-cell lysate  
*Strain:* B clade BRU *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1κ)**Ab Type** gp120 C5**Research Contact** Genetic Systems Corp, Seattle WA, E. Kinney-Thomas

**References** Maksiutov *et al.* 2002; Valenzuela *et al.* 1998; Binley *et al.* 1997a; McDougal *et al.* 1996; Cook *et al.* 1994; Moore *et al.* 1994c; Callahan *et al.* 1991; Pincus *et al.* 1991; Thomas *et al.* 1988; Linsley *et al.* 1988; Gosting *et al.* 1987

**Keywords** antibody binding site definition and exposure, immunotoxin

- 110.1 database comment: There is another antibody with this ID that binds to gp120, but at aa 200-217.
- 110.1: This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVP-TKADKRRSV. Maksiutov *et al.* [2002]
- 110.1: Does not effect LAI viral binding or entry into CEM cells. Valenzuela *et al.* [1998]
- 110.1: Does not neutralize HIV-1 LAI. McDougal *et al.* [1996]
- 110.1: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the carboxy-terminus of gp120 inhibit gp120 binding to GalCer but not as potently as anti-V3 MAbs – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]
- 110.1: The relative affinity for denatured/native gp120 is 0.7. Moore *et al.* [1994c] (**antibody binding site definition and exposure**)
- 110.1: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interactions mediated through the local high positive charge density in the V3 loop. The binding of this antibody is not inhibited by dextran sulfate, in contrast to anti-V3 antibodies. Callahan *et al.* [1991]
- 110.1: Difference was noted in the epitope: mapped to aa 421-429 (KQIINMWQE), the T1 sequence – poor efficacy as an immunotoxin when linked to RAC. Pincus *et al.* [1991] (**antibody binding site definition and exposure, immunotoxin**)
- 110.1: Referred to as 110-1 – does not inhibit CD4-gp120 binding or neutralize HIV-1 strains. Linsley *et al.* [1988]

**No.** 636**MAb ID** 42F**HXB2 Location** gp160 (491–500)**Author Location** gp120 (491–500 HXB2)**Epitope** IEPLGVAPTK**Subtype** B**Neutralizing** no**Immunogen** HIV-1 infection**Species (Isotype)** human (IgG1λ)**Ab Type** gp120 C5

**References** Maksiutov *et al.* 2002; Alsmadi & Tilley 1998; Alsmadi *et al.* 1997

- 42F: This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVPTKADKRRSV. Maksiutov *et al.* [2002]
- 42F: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against strains IIIB, MN, SF-2, and RF, but not a clone of MN. Alsmadi & Tilley [1998]
- 42F: 42F and 43F were isolated from a long term non-progressor by EBV transformation of PBMC – samples were taken 14 months apart – both MAbs stained diverse strains of infected cells and directed ADCC – were more potent for ADCC if the cell was infected with HIV-1, rather than just presenting absorbed gp120. Alsmadi *et al.* [1997]

**No.** 637**MAb ID** 43F**HXB2 Location** gp160 (491–500)**Author Location** gp120 (491–500 HXB2)**Epitope** IEPLGVAPTK**Subtype** B**Neutralizing** no**Immunogen** HIV-1 infection**Species (Isotype)** human (IgG1λ)**Ab Type** gp120 C5

**References** Maksiutov *et al.* 2002; Alsmadi *et al.* 1997

- 43F: This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVPTKADKRRSV. Maksiutov *et al.* [2002]
- 43F: 42F and 43F were isolated from a long term non-progressor by EBV transformation of PBMC – samples were taken 14 months apart – both MAbs stained diverse strains of infected cells and directed ADCC – were more potent for ADCC if the cell was infected with HIV-1, rather than just presenting absorbed gp120. Alsmadi *et al.* [1997]

**No.** 638**MAb ID** RV110026**HXB2 Location** gp160 (491–500)**Author Location** gp120 (491–500 LAI)**Epitope** IEPLGVAPTK**Subtype** B**Neutralizing****Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade LAI

**Species (Isotype)** human**Ab Type** gp120 C5**Research Contact** Commercial, Olympus Inc

**References** Maksiutov *et al.* 2002; Moore *et al.* 1994d; Moore *et al.* 1994c

- RV110026: This epitope is similar to a fragment of the human protein mast/stem cell growth factor receptor precursor, VVPTKADKRRSV. Maksiutov *et al.* [2002]
- RV110026: Preferentially binds SDS-DTT denatured gp120 (15 fold using R1/87 as capture reagent) Moore *et al.* [1994c]

**No.** 639**MAb ID** 105-306**HXB2 Location** gp160 (492–500)**Author Location** gp120 (HAM112, O group)**Epitope** KPFSVAPTP

**Neutralizing Immunogen** vaccine  
*Vector/Type:* protein *Strain:* O group  
 HAM112 *HIV component:* gp160

**Species (Isotype)** mouse (IgG1κ)

**Ab Type** C-term

**References** Scheffel *et al.* 1999

- 105-306: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity – 105-306 bound to two overlapping peptides. Scheffel *et al.* [1999]

**No.** 640

**MAb ID** GV1G2

**HXB2 Location** gp160 (494–499)

**Author Location** gp120 (494–499 IIIB)

**Epitope** LGVAPT

**Neutralizing Immunogen** vaccine  
*Vector/Type:* protein-Ab complex *HIV component:* gp120-Mab complex

**Species (Isotype)** mouse

**Ab Type** gp120 C5

**References** Denisova *et al.* 1996

- GV1G2: When anti-V3 MAb M77 was bound to gp120 and used as an immunogen, it stimulated many MAbs to linear epitopes – MAbs GV12F6 and GV3H1 are homologous to GV1G2 and were generated in the same experiment. Denisova *et al.* [1996]

**No.** 641

**MAb ID** 750-D

**HXB2 Location** gp160 (498–504)

**Author Location** gp120 (503–509)

**Epitope** PTKAKRR

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG3λ)

**Ab Type** C-term

**References** Hioe *et al.* 2000; Forthal *et al.* 1995

- 750-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – C5 MAbs 450-D and 750-D did not effect proliferation. Hioe *et al.* [2000]
- 750-D: Not neutralizing, positive ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995]

**No.** 642

**MAb ID** 450-D (450-D-3, 450D)

**HXB2 Location** gp160 (498–504)

**Author Location** gp120 (475–486 BH10)

**Epitope** PTKAKRR (orRRVVQRE, orMRDNWRSELYKY-dependenonreference)

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1λ)

**Ab Type** gp120 C5

**Research Contact** Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY

**References** Holl *et al.* 2006a; Verrier *et al.* 2001; Hioe *et al.* 2001; Hioe *et al.* 2000; Hioe *et al.* 1997b; Li *et al.* 1997; Manca *et al.* 1995a; Forthal *et al.* 1995; Cook *et al.* 1994; Gorny *et al.* 1994; Laal *et al.* 1994; Spear *et al.* 1993; Karwowska *et al.* 1992b; Karwowska *et al.* 1992a; Durda *et al.* 1988

**Keywords** dendritic cells, neutralization

- 450-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 450-D: CD4BS MAbs when complexed with gp120, inhibit proliferation of gp120-specific CD4 T-cells and IFN gamma production – 450-D does not have this effect and was used as a control in this study. Hioe *et al.* [2001]
- 450-D: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001]
- 450-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – C5 MAbs 450-D and 750-D did not effect proliferation. Hioe *et al.* [2000]
- 450-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b]
- 450-D: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – 50% neutralization could not be achieved at a maximal concentration of 6 mug/ml. Li *et al.* [1997]
- 450-D: No neutralizing activity, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995]
- 450-D: Virions complexed to gp120 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
- 450-D: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MAbs against the carboxy-terminus of gp120 do not inhibit gp120 binding to GalCer –

binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]

- 450-D: Epitope is defined as PTKAKRR. Gorny *et al.* [1994]
- 450-D: Not neutralizing alone, could synergize anti-CD4 binding site antibody neutralization. Laal *et al.* [1994]
- 450-D: Did not mediate deposition of complement component C3 on HIV infected cells. Spear *et al.* [1993]
- 450-D: Bound to MN, SF-2 and IIIB, but was not neutralizing. Karwowska *et al.* [1992a]

**No.** 643

**MAb ID** 670-D (670, 670D)

**HXB2 Location** gp160 (498–504)

**Author Location** gp120 (503–509)

**Epitope** PTKAKRR

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp120 C5

**Research Contact** Susan Zolla-Pazner (Zollas01@mccr6.med.nyu), NYU, NY

**References** Holl *et al.* 2006a; Gorny *et al.* 2005; Zwick *et al.* 2003; Verrier *et al.* 2001; Nyambi *et al.* 2000; Gorny & Zolla-Pazner 2000; Altmeyer *et al.* 1999; Nyambi *et al.* 1998; Gorny *et al.* 1998; Hioe *et al.* 1997b; Gorny *et al.* 1997; Hill *et al.* 1997; Forthal *et al.* 1995; Zolla-Pazner *et al.* 1995

**Keywords** antibody interactions, dendritic cells, neutralization

- 670D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 670: 2909 is a human anti-Env NAb that was selected by neutralization assay and binds to the quaternary structure on the intact virion. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670, 1418, nor 2G12. Gorny *et al.* [2005]
- 670-D: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C5-binding MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- 670-D: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001]

- 670-D: A gp120 C5 MAb used as a negative control in a study of anti-gp41 MAbs. Gorny & Zolla-Pazner [2000]
- 670-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 4 C5 MAbs, 2 bound well, 2 bound weakly – MAb 670-D bound 21/26, and was the most cross-reactive C5 MAb. Nyambi *et al.* [2000]
- 670-D: A Semliki Forest virus (SFV) expression system carrying BX08 env was used to study the conformation of gp120 – intracytoplasmic gp120 was recognized by the anti-V3 MAbs K24 and F5.5, while gp120 at the plasma membrane was detected only by conformation dependent MAbs 2G12, 670-D and 694/98D and not V3 MAbs – expression in rat brain also showed that surface-expressed Env was recognized only by the conformation-dependent antibodies and not by anti-V3 antibodies. Altmeyer *et al.* [1999]
- 670-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – anti-C5 Abs 670-D and 1331A bound to 3/4 B clade viruses (they didn't bind to IIIB), and to subtype D MAL – 670-D also reacted with subtype A. Nyambi *et al.* [1998]
- 670-D: gp120 can inhibit MIP-1alpha from binding to CCR5, but this inhibitory effect is blocked by pre-incubation of gp120 with three anti-V3 MAbs: 447, 257, 1027 – MAb 670 which binds in the C5 region had no effect. Hill *et al.* [1997]
- 670-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b]
- 670-D: Not neutralizing, positive ADCC activity, and no viral enhancing activity, numbering provided suggests epitope is RRVVQRE. Forthal *et al.* [1995]
- 670-D: Group specific cross-clade binding in serotyping study using flow-cytometry. Zolla-Pazner *et al.* [1995]

**No.** 644

**MAb ID** 158F3

**HXB2 Location** gp160 (499–511)

**Author Location** gp120 (BaL)

**Epitope** TKAKRRVQREKR

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* gp120-CD4 complex *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** humanized mouse (IgG2 $\kappa$ )

**Ab Type** C-term

**Research Contact** Abraham Pinter, Lab. of Retrovirology, Public Research Institute, pinter@phri.org

**References** He *et al.* 2003

**Keywords** antibody binding site definition and exposure, vaccine antigen design

- 158F3: Vaccination of a gp120-CD4 fusion complex in six transgenic XMG2 XenoMouse mice that produce human IgG2 with K light chain did not produce any neutralizing antibodies. 36/39 MAbs derived from one of these mice were in one of two competition groups that were conformational and specific for the complex, suggesting this chimeric vaccine may be of little value, as immunodominant responses are to epitopes unique to the complex, not present in native Env. This MAb is one of the 3/36 non-neutralizing MAbs that bound to linear epitopes on gp120. He *et al.* [2003] (**antibody binding site definition and exposure, vaccine antigen design**)

**No.** 645

**MAb ID** 161D7

**HXB2 Location** gp160 (499–511)

**Author Location** gp120 (BaL)

**Epitope** TKAKRRVVQREKR

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* gp120-CD4 complex *HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** humanized mouse (IgG2κ)

**Ab Type** C-term

**Research Contact** Abraham Pinter, Lab. of Retrovirology, Public Research Institute, pinter@phri.org

**References** He *et al.* 2003

**Keywords** antibody binding site definition and exposure, vaccine antigen design

- 161D7: Vaccination of a gp120-CD4 fusion complex in six transgenic XMG2 XenoMouse mice that produce human IgG2 with K light chain did not produce any neutralizing antibodies. 36/39 MAbs derived from one of these mice were in one of two competition groups that were conformational and specific for the complex, suggesting this chimeric vaccine may be of little value, as immunodominant responses are to epitopes unique to the complex, not present in native Env. This MAb is one of the 3/36 non-neutralizing MAbs that bound to linear epitopes on gp120. He *et al.* [2003] (**antibody binding site definition and exposure, vaccine antigen design**)

**No.** 646

**MAb ID** polyclonal

**HXB2 Location** gp160 (503–509)

**Author Location** gp120 (471–477)

**Epitope** RRVVQRE

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp120

**Species (Isotype)** mouse (IgG)

**References** Jeyarajah *et al.* 1998

- Mice were immunized with peptide APTKAKRRVVQREKR – epitope excision and extraction combined with mass spectrometry was used to map the fine structure of epitopes recognized by polyclonal Ab to HIV-1 Env – a major epitope

was identified between positions 472 and 478. Jeyarajah *et al.* [1998]

**No.** 647

**MAb ID** 722-D

**HXB2 Location** gp160 (503–509)

**Author Location** gp120 (503–509)

**Epitope** RRVVQRE

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** C-term

**References** Holl *et al.* 2006a; Forthal *et al.* 1995; Laal *et al.* 1994

**Keywords** dendritic cells, neutralization

- 722-D: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 722-D: No neutralizing activity, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995]
- 722-D: Not neutralizing alone, could synergize anti-CD4 binding site antibody neutralization. Laal *et al.* [1994]

**No.** 648

**MAb ID** polyclonal

**HXB2 Location** gp160 (503–511)

**Author Location** gp120 (508–516)

**Epitope** RRVVQREKR

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** C-term

**References** Loomis-Price *et al.* 1997; Palker *et al.* 1987

- Most HIV-1 + individuals have an antibody response to this epitope – in this study, reactivity to RRVVQREKR was used as a positive control for HIV-1 + gp160 vaccine recipients. Loomis-Price *et al.* [1997]

**No.** 649

**MAb ID** 1331A

**HXB2 Location** gp160 (503–511)

**Author Location** gp120 (510–516)

**Epitope** dwVVQREKR

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG3λ)

**Ab Type** gp120 C5

**Research Contact** Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu) (NYU Med. Center)

**References** Holl *et al.* 2006a; Zwick *et al.* 2003; Edwards *et al.* 2002; Gorny *et al.* 2002; Nyambi *et al.* 2000; Hochleitner *et al.* 2000b; Gorny *et al.* 2000; Nyambi *et al.* 1998

**Keywords** neutralization

- 1331A: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization**)

- 1331A: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C5-binding MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003]
- 1331A: Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002]
- 1331A: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions and the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control as binding was not diminished by treating gp120 with DTT or sodium metaperiodate to reduce disulfide bonds), and MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades). Gorny *et al.* [2002]
- 1331A: Core epitope dwVVQREKR maps to gp120(510-516) – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – C5 MAbs 858-D, 989-D and 1331A bound with a 5-10 fold preference for the monomer. Gorny *et al.* [2000]
- 1331A: The Ab binding site was studied with epitope excision (protein is bound in native conformation to immobilized MAb, then digested with proteolytic enzymes) and extraction (protein is digested then allowed to react with Ab), followed by mass spectroscopy – two non-contiguous aa in C5 were protected, E-507 and I-487, which are thought to be located on opposite sides of hydrophobic pocket involved in gp120/gp41 interaction. Hochleitner *et al.* [2000b]
- 1331A: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 4 C5 MAbs, 2 bound well, 2 bound weakly – MAb 858-D bound only 4/26, the worst of all anti-C5 MAbs tested, while MAb 1331A, which shares the same core epitope (positions 495-516), bound to 18/26. Nyambi *et al.* [2000]

- 1331A: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – anti-C5 Abs 670-D and 1331A bound to 3/4 B clade viruses (they don't bind to IIB), and to subtype D MAL. Nyambi *et al.* [1998]

**No.** 650

**MAb ID** 1131-A

**HXB2 Location** gp160 (505–511)

**Author Location** gp120 (510–516 LAI)

**Epitope** VVQREKR

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG3 $\lambda$ )

**Ab Type** C-term

**References** Bandres *et al.* 1998

- 1131-A: A very high affinity antibody used in studies that demonstrate that CXCR4 can bind to gp120 in the absence of CD4-gp120 interactions, and that this binding can be enhanced by Env deglycosylation. Bandres *et al.* [1998]

**No.** 651

**MAb ID** 858-D

**HXB2 Location** gp160 (505–511)

**Author Location** gp120 (510–516 LAI)

**Epitope** VVQREKR

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** C-term

**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrc6.med.nyu) (NYU Med. Center)

**References** Holl *et al.* 2006a; Nyambi *et al.* 2000; Gorny *et al.* 2000; Forthal *et al.* 1995; Zolla-Pazner *et al.* 1995

**Keywords** dendritic cells, neutralization

- 858-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 858-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – C5 MAbs 858-D, 989-D and 1331A bound with a 5-10 fold preference for the monomer. Gorny *et al.* [2000]
- 858-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 4 C5 MAbs, 2 bound well, 2 bound weakly – MAb 858-D bound only 4/26, the worst of all anti-C5 MAbs tested, while MAb 1331A, which shares the same core epitope (positions 495-516), bound to 18/26 isolates. Nyambi *et al.* [2000]
- 858-D: No neutralizing activity, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995]
- 858-D: Group specific cross-clade binding in serotyping study using flow-cytometry. Zolla-Pazner *et al.* [1995]



**No.** 652  
**MAb ID** 989-D  
**HXB2 Location** gp160 (505–511)  
**Author Location** gp120 (LAI)  
**Epitope** VVQREKR  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** C-term  
**Research Contact** Susan Zolla-Pazner (Zollas01@mccr6.med.nyu) (NYU Med. Center)  
**References** Nyambi *et al.* 2000; Gorny *et al.* 2000; Zolla-Pazner *et al.* 1995

- 989-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – C5 MAbs 858-D, 989-D and 1331A bound with a 5-10 fold preference for the monomer. Gorny *et al.* [2000]
- 989-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 4 C5 MAbs, 2 bound well, 2 bound weakly – MAb 989-D bound to 6/26 isolates. Nyambi *et al.* [2000]
- 989-D: In serotyping study using flow-cytometry, showed B clade specificity, but only reacted with 7/11 B clade virus. Zolla-Pazner *et al.* [1995]

**No.** 653  
**MAb ID** 1A1  
**HXB2 Location** gp160 (525–543)  
**Author Location** gp41 (526–543 BH10)  
**Epitope** AAGSTMGAASMTLVQARQ  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Research Contact** H. Katinger, Inst. Appl. Microbiol., Vienna, Austria  
**References** Maksiutov *et al.* 2002; Buchacher *et al.* 1994

- 1A1: This epitope is similar to a fragment of the HLA class II histocompatibility antigen, GGSCMAALTVTLTV. Maksiutov *et al.* [2002]
- 1A1: Human MAb generated using EBV transformation of PBL from HIV-1 + volunteers. Buchacher *et al.* [1994]

**No.** 654  
**MAb ID** 24G3  
**HXB2 Location** gp160 (525–543)  
**Author Location** gp41 (526–543 BH10)  
**Epitope** AAGSTMGAASMTLVQARQ  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Research Contact** H. Katinger, Inst. Appl. Microbiol., Vienna, Austria  
**References** Maksiutov *et al.* 2002; Buchacher *et al.* 1994; Buchacher *et al.* 1992

- 24G3: This epitope is similar to a fragment of the HLA class II histocompatibility antigen, GGSCMAALTVTLTV. Maksiutov *et al.* [2002]
- 24G3: Human MAb generated by electrofusion of PBL from HIV-1 + volunteers with CB-F7 cells. Buchacher *et al.* [1994]

**No.** 655  
**MAb ID** 25C2 (IAM 41-25C2)  
**HXB2 Location** gp160 (525–543)  
**Author Location** gp41 (526–543 BH10)  
**Epitope** AAGSTMGAASMTLVQARQ  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Research Contact** H. Katinger, Inst. Appl. Microbiol., Vienna, Austria and Viral Testing Systems, Houston, TX  
**References** Maksiutov *et al.* 2002; Sattentau *et al.* 1995; Buchacher *et al.* 1994; Buchacher *et al.* 1992

- 25C2: This epitope is similar to a fragment of the HLA class II histocompatibility antigen, GGSCMAALTVTLTV. Maksiutov *et al.* [2002]
- 25C2: Called IAM 41-25C2 – Binding domain overlaps sites that are critical for gp120-gp41 association – binding is enhanced by sCD4 – binding region defined as: gp41(21-38 BH10). Sattentau *et al.* [1995]
- 25C2: Human MAb generated by electrofusion of PBL from HIV-1 + volunteers with CB-F7 cells – binds oligomeric and monomeric gp41, and gp160. Buchacher *et al.* [1994]

**No.** 656  
**MAb ID** 5F3  
**HXB2 Location** gp160 (525–543)  
**Author Location** gp41 (526–543 BH10)  
**Epitope** AAGSTMGAASMTLVQARQ  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Research Contact** H. Katinger, Inst. Appl. Microbiol., Vienna, Austria  
**References** Holl *et al.* 2006a; Maksiutov *et al.* 2002; Buchacher *et al.* 1994  
**Keywords** dendritic cells, neutralization

- 5F3: This Ab did not inhibit HIV-1 BaL replication in macrophages. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 5F3: This epitope is similar to a fragment of the HLA class II histocompatibility antigen, GGSCMAALTVTLTV. Maksiutov *et al.* [2002]
- 5F3: Human MAb generated by electrofusion of PBL from HIV-1 + volunteers with CB-F7 cells. Buchacher *et al.* [1994]

**No.** 657  
**MAb ID** α(566-586)  
**HXB2 Location** gp160 (561–581)  
**Author Location** gp41 (566–586 BRU)  
**Epitope** AQQHLLQLTVWGIKQLQARIL  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human

**References** Poumbourios *et al.* 1992

**No.** 658  
**MAb ID** PC5009  
**HXB2 Location** gp160 (572–591)  
**Author Location** gp41 (577–596 BRU)  
**Epitope** GIKQLQARILAVERYLKDQQ  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp160  
**Species (Isotype)** mouse  
**References** Poumbourios *et al.* 1992  
 • PC5009: Recognized only monomeric gp41. Poumbourios *et al.* [1992]

**No.** 659  
**MAb ID** polyclonal  $\alpha$ 577-596  
**HXB2 Location** gp160 (572–591)  
**Author Location** gp41 (577–596 BRU)  
**Epitope** GIKQLQARILAVERYLKDQQ  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Poumbourios *et al.* 1992  
 • alpha(577-596): Affinity purified from HIV-1 + plasma – preferentially bind oligomer. Poumbourios *et al.* [1992]

**No.** 660  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (576–592)  
**Author Location** gp41 (583–599)  
**Epitope** LQARILAVERYLKDQQL  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Klasse *et al.* 1993b  
 • 42 HIV-1 positive human sera were tested against wildtype peptide, and peptide with substitution 589 A to T: 11/42 reacted strongly with wildtype, weakly with A589T – 31 reacted weakly with parental, even more weakly with substituted. Klasse *et al.* [1993b]

**No.** 661  
**MAb ID**  
**HXB2 Location** gp160 (577–583)  
**Author Location** gp41 (582–589)  
**Epitope** QARILAV  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** HIV-1 exposed seronegative  
**Species (Isotype)** human (IgA)  
**Ab Type** Leucine zipper motif  
**References** Clerici *et al.* 2002a

• Six sera from HIV-exposed uninfected individuals(EU), HIV-infected individuals and healthy controls were analyzed for IgA Abs – neutralizing activity was observed with total IgA from both EU and HIV+ – the EU IgA exclusively bound to a distinctive epitope within gp41, QARILAV, in the coiled coil pocket important for gp120-gp41 interactions – sera of QAFILAV-immunized BALB/c mice was neutralizing with the dose-dependent behavior similar to 2F5. Clerici *et al.* [2002a]

**No.** 662  
**MAb ID**  
**HXB2 Location** gp160 (577–583)  
**Author Location** gp41 (582–589)  
**Epitope** QARILAV  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* gp41 *Adjuvant:* Keyhole Limpit Haemocyanin (KLH)  
**Species (Isotype)** mouse (IgA)  
**Ab Type** Leucine zipper motif  
**References** Clerici *et al.* 2002a

• Six sera from HIV-exposed uninfected individuals(EU), HIV-infected individuals and healthy controls were analyzed for IgA Abs – neutralizing activity was observed with total IgA from both EU and HIV+ – the EU IgA exclusively bound to a distinctive epitope within gp41, QARILAV – sera of QAFILAV-immunized BALB/c mice was neutralizing with the dose-dependent behavior similar to 2F5. Clerici *et al.* [2002a]

**No.** 663  
**MAb ID** 1F11  
**HXB2 Location** gp160 (578–612)  
**Author Location** gp41 (579–613 BH10)  
**Epitope** ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\kappa$ )  
**Research Contact** H. Katinger, Inst. Appl. Microbiol., Vienna, Austria  
**References** Gorny & Zolla-Pazner 2004; Buchacher *et al.* 1994; Buchacher *et al.* 1992

**Keywords** antibody generation, review  
 • 1F11: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)  
 • 1F11: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

**No.** 664  
**MAb ID** 1H5  
**HXB2 Location** gp160 (578–612)  
**Author Location** gp41 (579–613 BH10)

**Epitope** ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**References** Gorny & Zolla-Pazner 2004; Buchacher *et al.* 1994; Buchacher *et al.* 1992  
**Keywords** antibody generation, review

- 1H5: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 1H5: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

**No.** 665  
**Mab ID** 3D9  
**HXB2 Location** gp160 (578–612)  
**Author Location** gp41 (579–613 BH10)  
**Epitope** ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Research Contact** H. Katinger, Inst. Appl. Microbiol., Vienna, Austria  
**References** Gorny & Zolla-Pazner 2004; Buchacher *et al.* 1994; Buchacher *et al.* 1992  
**Keywords** antibody generation, review

- 3D9: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 3D9: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

**No.** 666  
**Mab ID** 4B3  
**HXB2 Location** gp160 (578–612)  
**Author Location** gp41 (579–613 BH10)  
**Epitope** ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1λ)  
**Research Contact** H. Katinger, Inst. Appl. Microbiol., Vienna, Austria  
**References** Gorny & Zolla-Pazner 2004; Chen *et al.* 1994b; Buchacher *et al.* 1994; Buchacher *et al.* 1992  
**Keywords** antibody generation, review

- 4B3: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 4B3: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

**No.** 667  
**Mab ID** 4D4  
**HXB2 Location** gp160 (578–612)  
**Author Location** gp41 (579–613 BH10)  
**Epitope** ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1λ)  
**Research Contact** H. Katinger, Inst. Appl. Microbiol., Vienna, Austria and Viral Testing Systems, Houston, TX  
**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1999; Sattentau *et al.* 1995; Chen *et al.* 1994b; Buchacher *et al.* 1994; Buchacher *et al.* 1992

**Keywords** antibody binding site definition and exposure, antibody generation, review, vaccine antigen design

- 4D4: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 4D4: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**antibody binding site definition and exposure, vaccine antigen design**)
- 4D4: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

**No.** 668  
**Mab ID** 4G2  
**HXB2 Location** gp160 (578–612)  
**Author Location** gp41 (579–613 BH10)  
**Epitope** ARILAVERYLKDQQLLGIWGCSGKLICTTAVP-WNA  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Research Contact** H. Katinger, Inst. Appl. Microbiol., Vienna, Austria  
**References** Gorny & Zolla-Pazner 2004; Buchacher *et al.* 1994; Buchacher *et al.* 1992  
**Keywords** antibody generation, review

- 4G2: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 4G2: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

**No.** 669

**MAb ID** polyclonal

**HXB2 Location** gp160 (579–589)

**Author Location** gp41 (586–596 IIIB)

**Epitope** RILAVERYLKD

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41 *Adjuvant:* BSA

**Species (Isotype)** rabbit, mouse

**Ab Type** C-domain

**References** Xiao *et al.* 2000b

- Strong epitope-specific neutralizing antibody responses were induced using the peptide C(RILAVERYLKD)<sub>2</sub>-BSA, but not full gp160. Xiao *et al.* [2000b]

**No.** 670

**MAb ID** polyclonal

**HXB2 Location** gp160 (579–589)

**Author Location** gp41 (586–596)

**Epitope** RILAVERYLKD

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein, polyepitope *HIV component:* gp160 *Adjuvant:* BSA

**Species (Isotype)** rabbit

**Ab Type** N-term

**References** Lu *et al.* 2000b; Lu *et al.* 2000c

- High titer response to ELDKWA and RILAVERYLKD was observed upon vaccination with multiple-epitope vaccine CG-GPGRIFY-G-ELDKWA-G-RILAVERYLKD conjugated to BSA, a weak response to GPGRIFY – immunization with CG-(ELDKWA-GPGRIFY)<sub>2</sub>-K was also tried, yielding a strong Ab response to both ELDKWA and GPGRIFY – gp160 vaccination yielded strong Ab response but not to any of the peptides studied here. Lu *et al.* [2000c,b]

**No.** 671

**MAb ID**

**HXB2 Location** gp160 (579–599)

**Author Location** gp41 (586–606)

**Epitope** RILAVERYLKDQQLLGIWGCS

**Subtype** B

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Wang *et al.* 1986

**Keywords** assay standardization/improvement

- Immunoabsorbant peptide antigen RIAVERYLKDQQLLGIWGCS was used in a solid-phase enzyme immunoassay (EIA) to detect gp41-specific Abs in sera of virtually all HIV-1 infected individuals tested, with no false positives. This one 21 amino acid long peptide is recognized by sera from almost all AIDS patients, can be easily synthesized and employed for serological testing for HIV infection. Wang *et al.* [1986] (**assay standardization/improvement**)

**No.** 672

**MAb ID** polyclonal

**HXB2 Location** gp160 (579–599)

**Author Location** gp41 (583–604)

**Epitope** RILAVERYLKDQQLLGIWGCS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* desialylated gp160

**Species (Isotype)** rabbit

**References** Benjouad *et al.* 1993

- MAbs raised against desialylated HIV-1 gp160 cross-react with HIV-2 gp140 due to immunodominant conserved epitope in gp41. Benjouad *et al.* [1993]

**No.** 673

**MAb ID** 2A2/26

**HXB2 Location** gp160 (579–601)

**Author Location** gp41 (584–606 BRU)

**Epitope** RILAVERYLKDQQLLGIWGCSGK

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* gp41

**Species (Isotype)** mouse (IgG)

**References** Poubourios *et al.* 1995; Poubourios *et al.* 1992

- 2A2/26: Delta 550-561 (Delta LLRAIEAQQHLL), a region important for oligomer formation diminishes binding, Delta (550-561 +571-581) abrogates binding. Poubourios *et al.* [1995]
- 2A2/26: Immunodominant region, binds both oligomer and monomer. Poubourios *et al.* [1992]

**No.** 674

**MAb ID** 50-69 (SZ-50.69, 50-69D)

**HXB2 Location** gp160 (579–603)

**Author Location** gp41 (579–603 BH10)

**Epitope** RILAVERYLKDQQLLGIWGCSGKLI

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG2κ)

**Ab Type** gp41 cluster I

**Research Contact** Susan Zolla-Pazner (Zollas01@mrcr6.med.nyu), NYU, NY

**References** Holl *et al.* 2006a; Huang *et al.* 2007a; McCaffrey *et al.* 2004; Ling *et al.* 2004; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Follis *et al.* 2002; Verrier *et al.* 2001; Zwick *et al.* 2001b; Nyambi *et al.* 2000; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Mitchell

*et al.* 1998; Hioe *et al.* 1997b; Boots *et al.* 1997; Stamatatos *et al.* 1997; Klasse & Sattentau 1996; Binley *et al.* 1996; Poignard *et al.* 1996a; McDougal *et al.* 1996; Manca *et al.* 1995a; Sattentau *et al.* 1995; Chen *et al.* 1995; Laal *et al.* 1994; Spear *et al.* 1993; Edleston *et al.* 1993; Sattentau & Moore 1991; Robinson *et al.* 1991; Xu *et al.* 1991; Gorny *et al.* 1989; Pinter *et al.* 1989; Till *et al.* 1989

**Keywords** antibody binding site definition and exposure, antibody interactions, complement, dendritic cells, enhancing activity, immunotoxin, kinetics, mimotopes, neutralization, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 50-69: NIH AIDS Research and Reference Reagent Program: 531.
- 50-69: Increased binding of 50-69 Ab to gp41 in the presence of CD4 was abrogated by the small molecule HIV-1 entry inhibitor IC9564, suggesting that IC9564 arrests gp120 into a fusion-incompetent conformation unable to expose 50-69 epitope. Huang *et al.* [2007a] (**antibody binding site definition and exposure**)
- 50-69: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 50-69: This is one of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 50-69: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. gp41 MAbs 246D, 98.6, 50-69, were decreased by trypsin, unaltered by thrombin, while NAb 2F5 binding was increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 50-69: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. SF162 and each of the five glycosylation mutants studied were all neutralization resistant to 50-69. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure, vaccine antigen design**)
- 50-69: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D, 3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cytoplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure, kinetics**)
- 50-69: Called 50-69D. Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 sensitivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- 50-69: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**)
- 50-69: This paper primarily concerns 4E10 and Z13, MAbs that both bind proximally to the 2F5 binding site to a conserved epitope, and that neutralize some primary isolates from clades B, C, and E – MAb 50-69 binding to infected cells is enhanced by sCD4, while 4E10 and Z13 binding is essentially unaltered. Zwick *et al.* [2001b] (**antibody binding site definition and exposure**)
- 50-69: A cluster I epitope that binds to rgp41 567-647, recognizes a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41 – this MAb doesn't react with either of the peptides N51 or C43 individually – MAbs 50-69 and 1367 had similar properties –

- MAb 50-69 bound the fusogenic form of the protein in liquid phase. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 50-69: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
  - 50-69: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 cluster I anti-gp41 MAbs which showed good cross clade reactivity – 50-69 bound the majority of isolates although binding was moderate to weak – specifies discontinuous binding site range as aa 579-613. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 50-69: Mutations in BH10 gp160, W596Y and T605A, as well as deletions of 605-609 (TTAVP) and 597-609 (GC-SGKLICTTAVP), abrogate binding of enhancing MAbs 86, 240D, 50-69, and 246-D – 5/6 enhancing MAbs identified to date bind to the immunodominant region 579-613 – identifies non-contiguous W596-G597-C598 and C604-T605 as minimal epitope. Mitchell *et al.* [1998] (**antibody binding site definition and exposure**)
  - 50-69: Abs that recognize discontinuous epitopes can identify mimotopes from a phage peptide display library – 50-69 maps to an immunodominant domain in gp41 – three groups of peptides were selected, one which seems most closely related to gp41 sequence peptide consensus is WGCxx(RK)(x n)LxC – the analogous gp41 sequence WCGSGKLIK is present in most M group clades, except D with a common L to H substitution. Boots *et al.* [1997] (**mimotopes**)
  - 50-69: Binding of anti-gp120 MAbs IgG1b12 or 654-30D does not mediate significant exposure of the gp41 epitopes for MAbs 2F5 and 50-69. Stamatatos *et al.* [1997] (**antibody interactions**)
  - 50-69: Binds to a linear epitope located in the cluster I region – binding of 50-69 and 240-D inhibited by Fabs A1, A4, M8B, M26B, M12B and T2. Binley *et al.* [1996] (**antibody binding site definition and exposure**)
  - 50-69: Used to test exposure of gp41 upon sCD4 binding. Klasse & Sattentau [1996]
  - 50-69: Does not neutralize HIV-1 LAI. McDougal *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
  - 50-69: Prebinding of anti-V3, and CD4i MAbs 48d and 17b, but not anti-V2 neutralizing MAbs, expose the 50-69 epitope. Pognard *et al.* [1996a] (**antibody interactions**)
  - 50-69: One of several anti-gp41 MAbs that bind to a gp41-maltose binding fusion protein designed to study the leucine zipper domain of gp41, showing that the construct has retained aspects of normal gp41 conformation. Chen *et al.* [1995] (**antibody binding site definition and exposure**)
  - 50-69: Virions complexed to gp41 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
  - 50-69: Preferentially binds oligomer – binding increased after pretreatment of infected cells with sCD4 – binding domain overlaps site that is critical for gp120-gp41 association. Sattentau *et al.* [1995] (**antibody binding site definition and exposure**)
  - 50-69: Epitope described as cluster I, 601-604, conformational – does not neutralize IIIB or synergize neutralization by anti-V3 MAb 447-52D or by CD4 BS MAbs. Laal *et al.* [1994] (**antibody binding site definition and exposure, antibody interactions**)
  - 50-69: Called SZ-50.69 – binds to an epitope within aa 579-613. Eddleston *et al.* [1993] (**antibody binding site definition and exposure**)
  - 50-69: Did not mediate deposition of complement component C3 on HIV infected cells unless cells were pre-incubated with sCD4 – complement mediated virolysis of MN and IIIB in the presence of sCD4. Spear *et al.* [1993] (**complement**)
  - 50-69: Enhances HIV-1 infection *in vitro* – synergizes with huMAb 120-16 *in vitro* to enhance HIV-1 infection to level approaching that found in polyclonal anti-HIV serum. Robinson *et al.* [1991] (**antibody interactions, enhancing activity**)
  - 50-69: Two fold increase in binding to gp120 in the presence of bound sCD4. Sattentau & Moore [1991] (**antibody binding site definition and exposure**)
  - 50-69: The epitope is affected by the conformation conferred by the two cysteines at amino acids 598 and 604. Xu *et al.* [1991] (**antibody binding site definition and exposure**)
  - 50-69: Kills HIV-infected cells when coupled to deglycosylated ricin A chain. Gorny *et al.* [1989] (**immunotoxin**)
  - 50-69: Reacts preferentially with gp160 oligomer, compared to gp41 monomer. Pinter *et al.* [1989] (**antibody binding site definition and exposure**)
  - 50-69: Combined with deglycosylated A chain of ricin is toxic to lines of HIV-infected T cells (H9) and monocytes (U937). Till *et al.* [1989] (**immunotoxin**)
- No. 675**  
**MAb ID** 9-11  
**HXB2 Location** gp160 (579–604)  
**Author Location** gp41 (584–609)  
**Epitope** RILAVERYLKDQQLLGIWGCSGKLIK  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp160  
**Species (Isotype)** mouse (IgG1)  
**References** Mani *et al.* 1994
- 9-11: required the C-C disulfide bridge and loop formation, can bind simultaneously with 41-1. Mani *et al.* [1994]
- No. 676**  
**MAb ID** 98-43  
**HXB2 Location** gp160 (579–604)  
**Author Location** gp41 (579–604 HXB2)  
**Epitope** RILAVERYLKDQQLLGIWGCSGKLIK  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG2κ)  
**References** Xu *et al.* 1991; Tyler *et al.* 1990; Gorny *et al.* 1989; Pinter *et al.* 1989
- 98-43: NIH AIDS Research and Reference Reagent Program: 1241.

- 98-43: 579-604 binds in the immunodominant region. Xu *et al.* [1991]
- 98-43: Poor ADCC (in contrast to MAb 120-16, gp41(644-663)). Tyler *et al.* [1990]
- 98-43: Reacts equally well with oligomer and monomer. Pinter *et al.* [1989]

**No.** 677

**MAb ID** 41-1 (41.1)

**HXB2 Location** gp160 (579–608)

**Author Location** gp41 (584–609)

**Epitope** RILAVERYLKDQQLLGIWGCSGKLICTTAV

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* gp160

**Species (Isotype)** mouse (IgG1κ)

**References** Pincus *et al.* 1998; Pincus *et al.* 1996; Mani *et al.* 1994; Pincus & McClure 1993; Pincus *et al.* 1991; Dalgleish *et al.* 1988; Gosting *et al.* 1987

- 41-1 database comment: Also called 41.1, although possibly not, the literature is confusing because two gp41 MAbs that bind to this region with similar names (dash versus period) are listed as murine and human.
- 41-1: Called 41.1, and described as a human MAb, binding 579-604 – a panel of immunotoxins was generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996]
- 41-1: This antibody to gp41(584-609) Mani *et al.* [1994] seems to have been named the same as a different MAb to gp41(735-752 IIIB) Dalgleish *et al.* [1988]. Dalgleish *et al.* [1988]; Mani *et al.* [1994]
- 41-1: Did not require the C-C disulfide bridge and loop formation, can bind simultaneously with 9-11. Mani *et al.* [1994]
- 41-1: Called 41.1, and described as a human MAb – cross-competes with 41.4 – sCD4 enhances the efficacy of immunotoxins *in vitro* 30-fold – MAb was coupled to ricin A chain (RAC). Pincus & McClure [1993]
- 41-1: Efficacious as an immunotoxin when coupled to RAC – gave linear epitope as gp160 579-603. Pincus *et al.* [1991]
- 41-1: This antibody seems to have been named the same as a different MAb to gp41(735-752). Dalgleish *et al.* [1988]
- 41-1: Broadly reactive. Gosting *et al.* [1987]

**No.** 678

**MAb ID** 41.4

**HXB2 Location** gp160 (579–608)

**Author Location** gp41 (584–609)

**Epitope** RILAVERYLKDQQLLGIWGCSGKLICTTAV

**Neutralizing**

**Immunogen**

**Species (Isotype)**

**Research Contact** Jan McClure, Bristol-Myers Squibb Pharmaceutical Res Inst, Seattle, WA

**References** Pincus & McClure 1993

- 41.4: Binds to peptide weakly, but to gp160 with higher affinity than 41.1, and cross-competes with 41.1 – probably conformational – MAb was coupled to ricin A chain (RAC) – sCD4 enhances the efficacy of immunotoxins *in vitro* 30-fold. Pincus & McClure [1993]

**No.** 679

**MAb ID** Fab A1 (A1)

**HXB2 Location** gp160 (579–608)

**Author Location** gp41 (584–609 LAI)

**Epitope** RILAVERYLKDQQLLGIWGCSGKLICTTAV

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** anti-idiotypic, antibody generation, antibody sequence variable domain, review

- Fab A1: Called A1. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab A1: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**anti-idiotypic, antibody generation, antibody sequence variable domain**)

**No.** 680

**MAb ID** Fab A4 (A4)

**HXB2 Location** gp160 (579–608)

**Author Location** gp41 (584–609 LAI)

**Epitope** RILAVERYLKDQQLLGIWGCSGKLICTTAV

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab A4: Called A4. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab A4: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 681

**MAb ID** Fab M12B (M12B)

**HXB2 Location** gp160 (579–608)

**Author Location** gp41 (584–609 LAI)

**Epitope** RILAVERYLKDQQLLGIWGCSGKLICTTAV

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab M12B: Called M12B. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab M12B: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 682

**MAb ID** Fab M26B (M26B)

**HXB2 Location** gp160 (579–608)

**Author Location** gp41 (584–609 LAI)

**Epitope** RILAVERYLKDQQLLGIWGCSGKLICTTAV

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab M26B: Called M26B. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab M26B: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 683

**MAb ID** Fab M8B (M8B)

**HXB2 Location** gp160 (579–608)

**Author Location** gp41 (584–609 LAI)

**Epitope** RILAVERYLKDQQLLGIWGCSGKLICTTAV

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab M8B: Called M8B. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)

- Fab M8B: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 684

**MAb ID** Fab T2 (T2)

**HXB2 Location** gp160 (579–608)

**Author Location** gp41 (584–609 LAI)

**Epitope** RILAVERYLKDQQLLGIWGCSGKLICTTAV

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab T2: Called T2. One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- Fab T2: Binds to cluster I region – competes with MAbs 240-D and 50-69 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 685

**MAb ID** polyclonal

**HXB2 Location** gp160 (579–608)

**Author Location** gp41

**Epitope** RVAVERYLKDQQLLGIWGCSGKLICTTAV

**Subtype** D, multiple

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Barin *et al.* 2005

**Keywords** acute/early infection, assay development

- A combination of 4 antigenic regions was used to differentiate between early (<180 days) and chronic infection. These regions were: p24; the gp41 peptide spanning the immunodominant epitope (IDE) of gp41, RVAVERYLKDQQLLGIWGCSGKLICTTAV, and a subtype D version of this peptide; 5 V3 consensus peptides including A, B, C, D, and CRF01-AE; and Integrase. V3 and the IDE provide the best discrimination, with >20 fold higher levels in chronic infection when assayed by EIA using dried serum spots. Antibodies to Integrase and p24 were not as distinctive, and people tend to lose, not increase, responses to p24 over time. This assay can be used to identify samples from early infection with high sensitivity and specificity. Barin *et al.* [2005] (**assay development, acute/early infection**)

**No.** 686

**MAb ID** 86 (No. 86)

**HXB2 Location** gp160 (579–613)

**Author Location** gp41 (586–620 IIIB)



- Epitope** RILAVERYLKDQQLLGIWGCSGKLICTTAVPWNAS
- Neutralizing** no
- Immunogen** HIV-1 infection
- Species (Isotype)** human (IgG1κ)
- Research Contact** Evan Hersh and Yoh-Ichi Matsumoto
- References** Gorny & Zolla-Pazner 2004; Mitchell *et al.* 1998; Wisnewski *et al.* 1996; Moran *et al.* 1993; Pincus *et al.* 1991; Robinson *et al.* 1990c; Robinson *et al.* 1990b; Sugano *et al.* 1988
- Keywords** antibody binding site definition and exposure, antibody sequence variable domain, complement, enhancing activity, immunotoxin, review, variant cross-recognition or cross-neutralization
- 86: NIH AIDS Research and Reference Reagent Program: 380.
  - 86: This is one of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
  - 86: Mutations in BH10 gp160, W596Y and T605A, as well as deletions of 605-609 (TTAVP) and 597-609 (GCSGKLICTTAVP), abrogate binding of enhancing MAbs 86, 240D, 50-69, and 246-D – 5/6 enhancing MAbs identified to date bind to the immunodominant region 579-613. Mitchell *et al.* [1998] (**enhancing activity, variant cross-recognition or cross-neutralization**)
  - 86: 86 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
  - 86: Heavy (V H1) and light (V kappaI) chain sequenced – enhancing activity – similar germline sequence to MAb S1-1, but very different activity. Moran *et al.* [1993] (**enhancing activity, antibody sequence variable domain**)
  - 86: Poor immunotoxin activity when coupled to RAC – peptide binding stated to be aa 579-603. Pincus *et al.* [1991] (**antibody binding site definition and exposure, immunotoxin**)
  - 86: Antibody dependent enhancement (ADE) of HIV-1 IIIB infectivity in the presence of complement. Robinson *et al.* [1990b] (**complement, enhancing activity**)
  - 86: Peptide 586-620 blocks complement mediated ADE. Robinson *et al.* [1990c] (**enhancing activity**)
  - 86: Reacts with gp41 and also reacted weakly with gp120. Sugano *et al.* [1988] (**antibody binding site definition and exposure**)
- No.** 687
- MAb ID** polyclonal
- HXB2 Location** gp160 (580–597)
- Author Location** gp41 (584–602)
- Epitope** ILAVERYLKDQQLLGIWG
- Neutralizing** no
- Immunogen** HIV-1 infection
- Species (Isotype)** human
- References** Petrov *et al.* 1990
- Immunodominant and broadly reactive peptide. Petrov *et al.* [1990]
- No.** 688
- MAb ID** V10-9
- HXB2 Location** gp160 (580–613)
- Author Location** gp41 (586–620 IIIB)
- Epitope** ILAVERYLKDQQLLGIWGCSGKLICTTAVPWNAS
- Neutralizing** no
- Immunogen** HIV-1 infection
- Species (Isotype)** human (IgG1κ)
- References** Gorny & Zolla-Pazner 2004; Robinson *et al.* 1990c; Robinson *et al.* 1990b
- Keywords** antibody interactions, enhancing activity, review
- V10-9: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
  - V10-9: Antibody dependent enhancement (ADE) of HIV-1 IIIB infectivity, synergistically enhanced by MAb 120-16. Robinson *et al.* [1990b] (**antibody interactions, enhancing activity**)
  - V10-9: Peptide 586-620 blocks complement mediated ADE. Robinson *et al.* [1990c] (**enhancing activity**)
- No.** 689
- MAb ID** polyclonal
- HXB2 Location** gp160 (582–589)
- Author Location** gp41 (589–596)
- Epitope** AVERYLKD
- Neutralizing**
- Immunogen** HIV-1 infection
- Species (Isotype)** human
- References** Klasse *et al.* 1991
- Substitutions and deletions in peptide 583-599 were systematically studied – alterations in AVERYLKD abrogated the antigenicity of peptides with most of 14 human sera. Klasse *et al.* [1991]
- No.** 690
- MAb ID** anti-P1
- HXB2 Location** gp160 (582–592)
- Author Location** gp41 (579–613)
- Epitope** AVERYLKDQQL
- Subtype** B
- Neutralizing** no
- Immunogen** HIV-1 infection
- Species (Isotype)**
- References** Ferraz *et al.* 2004
- Keywords** assay development
- The B-cell epitope of P1 was incorporated into the solvent-exposed loop of the *E. coli* betagalactosidase enzyme for use as an analytical biosensor to permit enzyme substrate analysis to better understand the conversion of conformational stimulus into enzymatic signal. Ferraz *et al.* [2004] (**assay development**)
- No.** 691

**MAb ID** polyclonal  
**HXB2 Location** gp160 (584–604)  
**Author Location** gp41 (74–94)  
**Epitope** ERYLKDQLLGIWGCSGKLIC  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Shafferman *et al.* 1989  
 • Immunogenic domain useful for diagnostics. Shafferman *et al.* [1989]

**No.** 692  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (584–612)  
**Author Location** gp41 (587–617 BRU)  
**Epitope** ERYLKDQQLLGIWGCSGKLICTTAVPWNA  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Hernandez *et al.* 2000  
 • Chimeric peptide combining two peptides gp160(495-516 and 584-612) served as a specific and broadly reactive antigen for diagnostic detection of HIV-1. Hernandez *et al.* [2000]

**No.** 693  
**MAb ID** 2F11  
**HXB2 Location** gp160 (589–600)  
**Author Location** gp41 (589–600 HXB2)  
**Epitope** DQQLLGIWGCSG  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1)  
**References** Gorny & Zolla-Pazner 2004; Enshell-Seijffers *et al.* 2001; Eaton *et al.* 1994  
**Keywords** ADCC, enhancing activity, review  
 • 2F11: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)  
 • 2F11: Monoclonal antibodies to this epitope have distinct phenotypes—41-7 and 1B8.env were found to be not neutralizing, 2F11 possibly enhancing, and clone 3 beneficial. Enshell-Seijffers *et al.* [2001] (**enhancing activity**)  
 • 2F11: Enhances infectivity even in the absence of complement – does not mediate ADCC or neutralize virus. Eaton *et al.* [1994] (**ADCC, enhancing activity**)

**No.** 694  
**MAb ID** 246-D (SZ-246.D, 246, 246D)  
**HXB2 Location** gp160 (590–597)  
**Author Location** gp41 (579–604 HXB2)  
**Epitope** qqLLGIWg  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp41 cluster I

**Research Contact** Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU Med Center, NY, NY

**References** Holl *et al.* 2006a; Ling *et al.* 2004; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Follis *et al.* 2002; Edwards *et al.* 2002; Gorny *et al.* 2002; Verrier *et al.* 2001; Nyambi *et al.* 2000; Gorny & Zolla-Pazner 2000; Mitchell *et al.* 1998; Hioe *et al.* 1997b; Earl *et al.* 1997; Saarloos *et al.* 1995; Manca *et al.* 1995a; Forthal *et al.* 1995; Eddleston *et al.* 1993; Spear *et al.* 1993; Robinson *et al.* 1991; Xu *et al.* 1991

**Keywords** antibody binding site definition and exposure, antibody interactions, complement, dendritic cells, enhancing activity, kinetics, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 246-D: NIH AIDS Research and Reference Reagent Program: 1245.
- 246-D: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. It is also suggested that this Ab is directed against epitopes distinct from those recognized by NABs and that it will not impair virus entry into PBMCs but that it could participate in the protection of mucosal HIV transmission by preventing the infection of macrophages and iDCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 246-D: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 246-D: Called 246D. The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. gp41 MAbs 246D, 98.6, 50-69, were decreased by trypsin, unaltered by thrombin, while NAB 2F5 binding was increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 246-D: Called 246D – Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels

- of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**antibody binding site definition and exposure**)
- 246-D: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D, 3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cytoplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure, kinetics**)
  - 246-D: Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 sensitivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
  - 246-D: Called 246 – Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions and the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), and MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades tested, A, B, C, D, F and CRF01 (clade E). Gorny *et al.* [2002] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 246-D: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**)
  - 246-D: Core epitope aa 591 to 597, a cluster I epitope that does not bind to either a peptide complex that approximates the core of the fusogenic form of gp41 or the individual peptides N51 and C43 that form this structure – MAbs 181-D and 246-D had similar properties. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
  - 246-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 cluster I anti-gp41 MAbs which showed good cross clade reactivity – 246-D bound strongly or moderately to all 26 HIV-1 group M clades viruses tested and showed the strongest binding of all anti-Env MAbs tested, including the V3 and C5 region MAbs – notes core epitope as LLGI – no neutralizing activity was observed when 246-D was tested with five isolates. Nyambi *et al.* [2000] (**subtype comparisons**)
  - 246-D: Mutations in BH10 gp160, W596Y and T605A, as well as deletions of 605-609 (TTAVP) and 597-609 (GCSGK-LICTTAVP), abrogate binding of enhancing MAbs 86, 240D, 50-69, and 246-D – 5/6 enhancing MAbs identified to date bind to the immunodominant region 579-613. Mitchell *et al.* [1998] (**antibody binding site definition and exposure**)
  - 246-D: This antibody, along with murine MAb D61, can be blocked by any of a group of 8 conformational MAbs (M10, D41, D54, T4, T6, T9, T10 and T35). Earl *et al.* [1997] (**antibody interactions**)
  - 246-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations and 246-D neutralized 91US056 – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
  - 246-D: No neutralizing activity, both ADCC and viral enhancing activity. Forthal *et al.* [1995] (**complement, enhancing activity**)
  - 246-D: Virions complexed to gp41 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
  - 246-D: Ab-mediated activation of complement on HIV+ cells is higher than Ab independent activation—what has been termed “Ab independent” in fact results in part from IgM in normal human serum that is HIV-cross-reactive. Saarloos *et al.* [1995] (**complement**)
  - 246-D: Called SZ-246.D. Eddleston *et al.* [1993]
  - 246-D: Did not mediate deposition of complement component C3 on HIV infected cells unless cells were pre-incubated with sCD4. Spear *et al.* [1993] (**complement**)

- 246-D: No neutralizing activity, some enhancing activity. Robinson *et al.* [1991] (**enhancing activity**)
- 246-D: Fine mapping indicates core is LLGI. Xu *et al.* [1991] (**antibody binding site definition and exposure**)

No. 695

**MAb ID** polyclonal  
**HXB2 Location** gp160 (590–607)  
**Author Location** gp41  
**Epitope** QLLGIWGCSCGKLICTTA  
**Subtype** B, CRF01\_AE  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**References** Parekh *et al.* 2002

- A simple enzyme immunoassay (EIA) that detects increasing levels of anti-HIV IgG after seroconversion can be used for detecting recent HIV-1 infection – longitudinal specimens from 139 incident infections in the US and Thailand were used in the study – the method was generally applicable for HIV-1 subtypes A, B, C, D and E(CRF01). Parekh *et al.* [2002]

No. 696

**MAb ID** 9G5A  
**HXB2 Location** gp160 (591–594)  
**Author Location** gp41 (596–599 IIIB)  
**Epitope** QLLG  
**Neutralizing**  
**Immunogen** anti-idiotype  
**Species (Isotype)** mouse (IgM)  
**References** Beretta & Dalgleish 1994; Lopalco *et al.* 1993  
 • 9G5A: Anti-idiotype to gp120 C terminus (C5 region) MAb M38. Lopalco *et al.* [1993]

No. 697

**MAb ID** 181-D (SZ-181.D)  
**HXB2 Location** gp160 (591–597)  
**Author Location** gp41 (591–597 HXB2)  
**Epitope** qLLGIWg  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG2κ)  
**Ab Type** gp41 cluster I  
**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu), NYU, NY

**References** Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Gorny & Zolla-Pazner 2000; Fontenot *et al.* 1995; Forthal *et al.* 1995; Eddleston *et al.* 1993; Robinson *et al.* 1991; Xu *et al.* 1991

**Keywords** ADCC, antibody binding site definition and exposure, dendritic cells, enhancing activity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 181-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)

- 181-D: This is one of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 181-D: Core epitope aa 591 to 597, a cluster I epitope that does not bind to either a peptide complex that approximates the core of the fusogenic form of gp41 or the individual peptides N51 and C43 that form this structure – MAbs 181-D and 246-D had similar properties. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 181-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 cluster I anti-gp41 MAbs which showed good cross clade reactivity – 181-D bound the majority of isolates although binding was moderate to weak. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- 181-D: No neutralizing, no ADCC, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC, enhancing activity**)
- 181-D: Called SZ-181.D. Eddleston *et al.* [1993]
- 181-D: No enhancing or neutralization activity. Robinson *et al.* [1991] (**enhancing activity**)
- 181-D: Fine mapping indicates core is LLGIW. Xu *et al.* [1991] (**antibody binding site definition and exposure**)

No. 698

**MAb ID** 240-D (F240)  
**HXB2 Location** gp160 (592–600)  
**Author Location** gp41 (592–600 HXB2)  
**Epitope** LLGIWGCSCG  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp41 cluster I  
**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu), NYU, NY

**References** Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Nyambi *et al.* 2000; Mitchell *et al.* 1998; Wisniewski *et al.* 1996; Wisniewski *et al.* 1995; Binley *et al.* 1996; Spear *et al.* 1993; Robinson *et al.* 1991; Xu *et al.* 1991

**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, complement, dendritic cells, enhancing activity, kinetics, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 240-D: NIH AIDS Research and Reference Reagent Program: 1242.
- 240-D: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. It is also suggested that this Ab is directed against epitopes distinct from those recognized by NABs and that it will

not impair virus entry into PBMCs but that it could participate in the protection of mucosal HIV transmission by preventing the infection of macrophages and iDCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)

- 240-D: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 240-D: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D, 3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cytoplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure, kinetics**)
- 240-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 cluster I anti-gp41 MAbs which showed good cross clade reactivity – 246-D bound strongly or moderately to 24/26 HIV-1 group M clades viruses tested. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- 240-D: Mutations in BH10 gp160, W596Y and T605A, as well as deletions of 605-609 (TTAVP) and 597-609 (GCSGK-LICTTAVP), abrogate binding of enhancing MAbs 86, 240D, 50-69, and 246-D – 5/6 enhancing MAbs identified to date bind to the immunodominant region 579-613. Mitchell *et al.* [1998] (**enhancing activity**)
- 240-D: Binds to a linear epitope located in the cluster I region – binding of 50-69 and 240-D inhibited by Fabs A1, A4, M8B, M26B, M12B and T2. Binley *et al.* [1996] (**antibody binding site definition and exposure**)
- 240-D: V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996] (**antibody sequence variable domain**)
- 240-D: Did not mediate deposition of complement component C3 on HIV infected cells. Spear *et al.* [1993] (**complement**)
- 240-D: No neutralizing activity, some enhancing activity. Robinson *et al.* [1991] (**enhancing activity**)
- 240-D: Fine mapping indicates core is IWG. Xu *et al.* [1991] (**antibody binding site definition and exposure**)

No. 699

MAb ID F240

**HXB2 Location** gp160 (592–606)

**Author Location** gp41 (592–606 BH10)

**Epitope** LLGIWGC SGKLICTT

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster I

**Research Contact** L. Cavacina or M. Posner, Dept. of Med. Harvard Med. School, Boston MA, USA

**References** Holl *et al.* 2006a; Liu *et al.* 2005a; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Follis *et al.* 2002; Cavacini *et al.* 2003; Cavacini *et al.* 2002; York *et al.* 2001; Cavacini *et al.* 1998a

**Keywords** antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, co-receptor, dendritic cells, enhancing activity, neutralization, review, variant cross-recognition or cross-neutralization

- F240: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. It is also suggested that this Ab is directed against epitopes distinct from those recognized by NAb and that it will not impair virus entry into PBMCs but that it could participate in the protection of mucosal HIV transmission by preventing the infection of macrophages and iDCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- F240: Transduction of human CD4+ H9 T cells with both the intracellularly expressed and secreted forms of the single-chain F240 Ab inhibited MN virus production. The secreted form was more potent. Viral replication of HIV-1 primary isolates was not reduced. Liu *et al.* [2005a]
- F240: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- F240: The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. Anti-gp41 MAb F240 could inhibit B4e8 neutralization. Cavacini *et al.* [2003] (**antibody interactions**)
- F240: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate, with the exception of F240 which bound both equally well, which captured more virus than any other human MAb tested, and didn't neutralize either isolate. F240 enhanced the binding of CD4BS MAbs IgG1b12 and F105 and the gp41 MAb 2F5 for both R5X4 and R5 isolates. F240 binding to gp41 was not affected by the binding of the V3 loop MAb B4a1, but preincubation with F240 could enhance B4a1 binding of the R5 isolate. Synergistic neutralization between F240 and CD4i MAbs 17b and 48d was noted for the R5X4 but not the R5 isolate, and F240 also enhanced neutralization of the R5X4 isolate by 2F5, but had

no effect on R5 virus. In contrast, F240 combined with 2G12 demonstrated enhanced neutralization of R5 virus at low Ab concentrations. Cavacini *et al.* [2002] (**antibody interactions, co-receptor**)

- F240: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D, 3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cytoplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure**)
- F240: Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 sensitivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- F240: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAb alters some step after binding. York *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
- F240: Distinct from MAb 240-D, an antibody with a similar epitope in the immunodominant region of gp41 – dose-dependent reactivity with HIV isolates RF, SF2, IIIB, and MN was observed – F240 had no neutralizing activity and enhances infection in the presence of complement – reactivity of F240 is enhanced by preincubation of cells with sCD4 or anti-CD4BS MAb F105 – heavy and light chain variable domains were sequenced, and a strong homology to hu MAb 3D6 was observed, as 3D6 binds to the same epitope, these MAbs may define a human Ab clonotype. Cavacini *et al.*

[1998a] (**enhancing activity, variant cross-recognition or cross-neutralization, antibody sequence variable domain**)

**No.** 700

**MAb ID** D49

**HXB2 Location** gp160 (592–608)

**Author Location** gp41 (597–613)

**Epitope** LLGIWGC SGKLICTTAV

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* dimeric Env

**Species (Isotype)** mouse

**Ab Type** gp41 cluster I

**Research Contact** Pat Earl

**References** Dimitrov *et al.* 2007; Earl *et al.* 1997; Earl *et al.* 1994

**Keywords** kinetics

- D49: In contrast to a decrease of 2F5 and 4E10 binding upon triggering of HIV-1 Env-expressing cells with target cells, binding of D49 to its epitope in the immunodominant loop of gp41 remains unchanged, indicating that the decrease seen for 2F5 and 4E10 is not due to removal of gp41 from the surface. Dimitrov *et al.* [2007] (**kinetics**)
- D49: Binding maps to region 597-613: WGCSGKLICT-TAVPWNA – immunodominant region containing two Cys residues. Earl *et al.* [1997]
- D49: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 701

**MAb ID** D61

**HXB2 Location** gp160 (592–608)

**Author Location** gp41 (592–608 HXB2)

**Epitope** LLGIWGC SGKLICTTAV

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* dimeric Env

**Species (Isotype)** mouse

**Ab Type** gp41 cluster I

**Research Contact** Patricia Earl and Christopher Broder, NIH

**References** Golding *et al.* 2002b; Earl *et al.* 1997; Weisenhorn *et al.* 1996; Richardson *et al.* 1996; Earl *et al.* 1994

**Keywords** antibody binding site definition and exposure, antibody generation

- D61: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b – nor did it alter two gp41 MAbs, T9 and D61, inability to inhibit fusion. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)

- D61: Binding maps to region 597-613: WGCSGKLICT-TAVPWNA – immunodominant region containing two Cys residues – this antibody, along with human MAb 246-D, can be blocked by any of a group of 8 conformational MAbs (M10, D41, D54, T4, T6, T9, T10 and T35) – members of this competition group are blocked by sera from HIV-1 + individuals. Earl *et al.* [1997] (**antibody binding site definition and exposure**)
- D61: Linear gp41 epitope in the cluster I region – human sera blocked binding in oligomeric ELISA assay to a similar extent for gp41 MAbs D20, D43, D61, and T4. Richardson *et al.* [1996] (**antibody binding site definition and exposure**)
- D61: Does not precipitate gp41(21-166), but due to a structural difference in the disulfide bonding region near the two cysteines – the authors propose that this region may change conformation during the activation of the membrane fusion state of the HIV-1 glycoprotein. Weissenhorn *et al.* [1996] (**antibody binding site definition and exposure**)
- D61: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 702

MAb ID T32

HXB2 Location gp160 (592–608)

Author Location gp41 (597–613)

Epitope LLGIWGCSGKLICTTAV

Neutralizing

Immunogen vaccine

Vector/Type: tetrameric Env HIV component: Env

Species (Isotype) mouse

Ab Type gp41 cluster I

Research Contact Patricia Earl and Christopher Broder, NIH

References Earl *et al.* 1997; Earl *et al.* 1994

- T32: Binding maps to region 597-613: WGCSGKLICT-TAVPWNA – immunodominant region containing two Cys residues. Earl *et al.* [1997]
- T32: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 703

MAb ID T34

HXB2 Location gp160 (592–608)

Author Location gp41 (597–613)

Epitope LLGIWGCSGKLICTTAV

Neutralizing

Immunogen vaccine

Vector/Type: tetrameric Env HIV component: Env

Species (Isotype) mouse

Ab Type gp41 cluster I

Research Contact Patricia Earl and Christopher Broder, NIH

References Earl *et al.* 1997; Earl *et al.* 1994

- T34: Binding maps to region 597-613: WGCSGKLICT-TAVPWNA – immunodominant region containing two Cys residues. Earl *et al.* [1997]

- T34: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response – an oligomer with no gp120/gp41 cleavage site was used as the immunogen. Earl *et al.* [1994]

No. 704

MAb ID 115.8

HXB2 Location gp160 (593–604)

Author Location gp41 (598–609)

Epitope LGLIWGCSGKLICT

Neutralizing

Immunogen vaccine

Vector/Type: peptide HIV component: gp41

Species (Isotype) mouse (IgM)

References Oldstone *et al.* 1991

- 115.8: Stimulated by immunization with the peptide: LGLIWGCSGKLICT (aa 598-609) – poor reactivity with CSGKLICT – reacts well with longer HIV-2 peptide NSWGCAFRQVC as well as CAFRQVC – disulfide bond between cysteines required. Oldstone *et al.* [1991]

No. 705

MAb ID M-1

HXB2 Location gp160 (593–604)

Author Location gp41 (598–609)

Epitope LGIWGCSGKLICT

Neutralizing

Immunogen vaccine

Vector/Type: peptide HIV component: gp41

Species (Isotype) mouse (IgG1, IgG2b)

References Yamada *et al.* 1991

- M-1: Unlike M-22, did not react to 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

No. 706

MAb ID M-11

HXB2 Location gp160 (593–604)

Author Location gp41 (598–609)

Epitope LGIWGCSGKLICT

Neutralizing

Immunogen vaccine

Vector/Type: peptide HIV component: gp41

Species (Isotype) mouse (IgG1)

References Yamada *et al.* 1991

- M-11: Strongly reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

No. 707

MAb ID M-13

HXB2 Location gp160 (593–604)

Author Location gp41 (598–609)

Epitope LGIWGCSGKLICT

Neutralizing

Immunogen vaccine

Vector/Type: peptide HIV component: gp41

**Species (Isotype)** mouse (IgG2b)

**References** Yamada *et al.* 1991

- M-13: Reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

**No.** 708

**MAb ID** M-2

**HXB2 Location** gp160 (593–604)

**Author Location** gp41 (598–609)

**Epitope** LGIWGCSGKLIC

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41

**Species (Isotype)** mouse (IgG2b)

**References** Yamada *et al.* 1991

- M-2: Strongly reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

**No.** 709

**MAb ID** M-22

**HXB2 Location** gp160 (593–604)

**Author Location** gp41 (598–609)

**Epitope** LGIWGCSGKLIC

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41

**Species (Isotype)** mouse (IgG2b)

**References** Yamada *et al.* 1991

- M-22: Strongest reaction of 12 anti-HIV-1 gp41 MAbs to a cellular 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

**No.** 710

**MAb ID** M-24

**HXB2 Location** gp160 (593–604)

**Author Location** gp41 (598–609)

**Epitope** LGIWGCSGKLIC

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41

**Species (Isotype)** mouse (IgG1)

**References** Yamada *et al.* 1991

- M-24: Strongly reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

**No.** 711

**MAb ID** M-25

**HXB2 Location** gp160 (593–604)

**Author Location** gp41 (598–609)

**Epitope** LGIWGCSGKLIC

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41

**Species (Isotype)** mouse (IgG1)

**References** Yamada *et al.* 1991

- M-25: Reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

**No.** 712

**MAb ID** M-28

**HXB2 Location** gp160 (593–604)

**Author Location** gp41 (598–609)

**Epitope** LGIWGCSGKLIC

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41

**Species (Isotype)** mouse (IgG1)

**References** Yamada *et al.* 1991

- M-28: Strongly reacted with a cellular 43-kd protein found in rat and human astrocytes as well as with gp41. Yamada *et al.* [1991]

**No.** 713

**MAb ID** M-29

**HXB2 Location** gp160 (593–604)

**Author Location** gp41 (598–609)

**Epitope** LGIWGCSGKLIC

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41

**Species (Isotype)** mouse (IgG1)

**References** Yamada *et al.* 1991

- M-29: Unlike M-22, did not react to 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

**No.** 714

**MAb ID** M-36

**HXB2 Location** gp160 (593–604)

**Author Location** gp41 (598–609)

**Epitope** LGIWGCSGKLIC

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41

**Species (Isotype)** mouse (IgG1)

**References** Yamada *et al.* 1991

- M-36: Unlike M-22, did not react to 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

**No.** 715

**MAb ID** M-4

**HXB2 Location** gp160 (593–604)

**Author Location** gp41 (598–609)

**Epitope** LGIWGCSGKLIC

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41

**Species (Isotype)** mouse (IgG2b)

**References** Yamada *et al.* 1991

- M-4: Unlike M-22, did not react to 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]



**No.** 716  
**MAb ID** M-6  
**HXB2 Location** gp160 (593–604)  
**Author Location** gp41 (598–609)  
**Epitope** LGIWGCSGKLIC  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* gp41  
**Species (Isotype)** mouse (IgG2b)  
**References** Yamada *et al.* 1991  
 • M-6: Unlike M-22, did not react to 43-kd protein found in rat and human astrocytes. Yamada *et al.* [1991]

**No.** 717  
**MAb ID** polyclonal  $\alpha$ 598-609  
**HXB2 Location** gp160 (594–601)  
**Author Location** gp41 (598–609)  
**Epitope** GIWGCSGK  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Poumbourios *et al.* 1992  
 • alpha(598-609): Affinity purified from HIV-1 + plasma – immunodominant region, binds oligomer and monomer. Poumbourios *et al.* [1992]

**No.** 718  
**MAb ID** 1B8.env (1B8)  
**HXB2 Location** gp160 (594–604)  
**Author Location** gp41 (594–605 HXB2)  
**Epitope** GIWGCSGKLIC  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG2 $\lambda$ )  
**References** Gorny & Zolla-Pazner 2004; Enshell-Seijffers *et al.* 2001; Banapour *et al.* 1987  
**Keywords** antibody binding site definition and exposure, review, variant cross-recognition or cross-neutralization  
 • 1B8B.env: Called 1B8. There are 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)  
 • 1B8.env: Monoclonal antibodies to this epitope have distinct phenotypes—41-7 and 1B8.env were found to be not neutralizing, 2F11 possibly enhancing, and clone 3 beneficial. Enshell-Seijffers *et al.* [2001]  
 • 1B8.env: Highly conserved epitope recognized by the majority of HIV-1 infected people – MAb does not neutralize. Banapour *et al.* [1987] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)

**No.** 719  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (594–609)  
**Author Location** gp41 (601–616)  
**Epitope** GIWGCSGKLICTTAVP  
**Neutralizing** no

**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Petrov *et al.* 1990  
 • Immunodominant and broadly reactive peptide. Petrov *et al.* [1990]

**No.** 720  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (595–607)  
**Author Location** gp41 (600–612)  
**Epitope** IWGCSGKLICTTA  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**References** Belliard *et al.* 2003  
**Keywords** rate of progression  
 • Sera from 101 slow progressors and 42 fast progressors were tested for responses to Tat peptides, and compared to responses to gp41 peptide 600-612, as anti-Tat antibodies had been shown by others to be elevated in slow progressors. Most patient sera react with this peptide, it is used in diagnostics. In this study, overall levels of Tat antibodies were not different in the two groups, however relative levels of antibodies to different Tat peptides and to this gp41 peptide were observed. Belliard *et al.* [2003] (**rate of progression**)

**No.** 721  
**MAb ID** clone 3 (CL3)  
**HXB2 Location** gp160 (597–606)  
**Author Location** gp41 (597–606)  
**Epitope** GCSGKLICTT  
**Subtype** B  
**Neutralizing** L P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1)  
**Research Contact** BioClonetics (Philadelphia)  
**References** Ferrantelli *et al.* 2004a; Gorny & Zolla-Pazner 2004; Enshell-Seijffers *et al.* 2001; Cotropia *et al.* 1996; Cotropia *et al.* 1992; Brolden *et al.* 1989  
**Keywords** antibody binding site definition and exposure, rate of progression, responses in children, review, subtype comparisons, variant cross-recognition or cross-neutralization  
 • clone 3: Called CL3 here. Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. Clone 3 could neutralize some O group strains. CL3 is specific for a linear epitope containing 2 cysteines that generate a loop that could be important during the fusion of the virus with the target cell. This epitope is represented as GCxGxxxCxT HIV-1 group O isolates. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)  
 • clone 3: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. clone 3 neutralized 3 diverse B clade TCLA strains and 3 primary O group strains. Gorny & Zolla-Pazner [2004] (**variant**)

**cross-recognition or cross-neutralization, review, subtype comparisons)**

- clone 3: Monoclonal antibodies to this epitope have distinct phenotypes—41-7 and 1B8.env were found to be not neutralizing, 2F11 possibly enhancing, and clone 3 beneficial. Enshell-Seijffers *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
- clone 3: Inhibits replication of three diverse HIV-1 laboratory strains, as well as an AZT-resistant isolate. Cotropia *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
- clone 3: Core binding domain gcskLIC – lack of serological activity to this region correlates with rapid progression in infants (Broliden *et al.* [1989]) Cotropia *et al.* [1992]. Broliden *et al.* [1989]; Cotropia *et al.* [1992] (**antibody binding site definition and exposure, responses in children, rate of progression**)

No. 722

Mab ID 4

HXB2 Location gp160 (598–604)

Author Location gp41 (598–609)

Epitope CSGKLIC

Neutralizing

Immunogen vaccine

*Vector/Type:* peptide HIV component: gp41

Species (Isotype) mouse (IgG2b)

References Bizub-Bender *et al.* 1994; Oldstone *et al.* 1991

- There is another MAb with this ID that reacts with integrase. Bizub-Bender *et al.* [1994]; Oldstone *et al.* [1991]
- 4: Stimulated by immunization with the peptide: LGLIWGCSGKLIC (aa 598-609) – poor cross-reactivity with HIV-2 peptide CAFRQVC – slightly more reactive with longer HIV-2 peptide NSWGCAFRQVC. Oldstone *et al.* [1991]

No. 723

Mab ID 41-6

HXB2 Location gp160 (598–604)

Author Location gp41 (598–609)

Epitope CSGKLIC

Neutralizing

Immunogen vaccine

*Vector/Type:* peptide HIV component: gp41

Species (Isotype) mouse (IgG2b)

References Oldstone *et al.* 1991

- 41-6: Stimulated by immunization with the peptide: LGLIWGCSGKLIC (aa 598-609) – poor cross-reactivity with HIV-2 peptide CAFRQVC – slightly more reactive with LGLIWGCSGKLIC and HIV-2 form NSWGCAFRQVC – disulfide bond between cysteines required. Oldstone *et al.* [1991]

No. 724

Mab ID 41-7

HXB2 Location gp160 (598–604)

Author Location gp41 (605–611)

Epitope CSGKLIC

Neutralizing no

Immunogen HIV-1 infection

Species (Isotype) human (IgG1κ)

References Enshell-Seijffers *et al.* 2001; Bugge *et al.* 1990

- 41-7: Monoclonal antibodies to this epitope have distinct phenotypes—41-7 and 1B8.env were found to be not neutralizing, 2F11 possibly enhancing, and clone 3 beneficial. Enshell-Seijffers *et al.* [2001]
- 41-7: Sera from 6/6 HIV-1 positive, but no HIV-2 positive individuals, interfered with 41-7 binding – Ab does not neutralize. Bugge *et al.* [1990]

No. 725

Mab ID 68.1

HXB2 Location gp160 (598–604)

Author Location gp41 (598–609)

Epitope CSGKLIC

Neutralizing

Immunogen vaccine

*Vector/Type:* peptide HIV component: gp41

Species (Isotype) mouse (IgM)

References Oldstone *et al.* 1991

- 68.1: Stimulated by immunization with the peptide: LGLIWGCSGKLIC (aa 598-609) – cross-reactive with HIV-2 peptide CAFRQVC – more reactive with longer HIV-1 peptide LGLIWGCSGKLIC and HIV-2 peptide NSWGCAFRQVC. Oldstone *et al.* [1991]

No. 726

Mab ID 68.11

HXB2 Location gp160 (598–604)

Author Location gp41 (598–609)

Epitope CSGKLIC

Neutralizing

Immunogen vaccine

*Vector/Type:* peptide HIV component: gp41

Species (Isotype) mouse (IgM)

References Oldstone *et al.* 1991

- 68.11: Stimulated by immunization with the peptide: LGLIWGCSGKLIC (aa 598-609) – cross-reactive with HIV-2 peptide CAFRQVC – more reactive with longer HIV-1 peptide LGLIWGCSGKLIC and HIV-2 peptide NSWGCAFRQVC. Oldstone *et al.* [1991]

No. 727

Mab ID 75

HXB2 Location gp160 (598–604)

Author Location gp41 (598–609)

Epitope CSGKLIC

Neutralizing

Immunogen vaccine

*Vector/Type:* peptide HIV component: gp41

Species (Isotype) rat (IgG)

References Oldstone *et al.* 1991

- 75: Stimulated by immunization with the peptide: LGLI-WGCSGKLIIC (aa 598-609) – poor cross-reactivity with HIV-2 peptide CAFRQVC – more reactive with longer HIV-2 peptide NSWGCAFRQVC. Oldstone *et al.* [1991]

No. 728

**MAb ID** polyclonal  
**HXB2 Location** gp160 (598–604)  
**Author Location** gp41 (603–609)  
**Epitope** CSGKLIIC  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Enshell-Seiffers *et al.* 2001

- Monoclonal antibodies to this epitope have distinct phenotypes – 41-7 and 1B8.env were found to be not neutralizing, 2F11 possibly enhancing, and clone 3 beneficial – isolated mimotope-presenting phages corresponding to the immunodominant gp41 epitope CSGKLIIC were used to study the diversity of polyclonal responses in 30 HIV+ sera, and all but one of the patients reacted showing distinctive variable polyclonal recognition patterns. Enshell-Seiffers *et al.* [2001]

No. 729

**MAb ID** 105-732  
**HXB2 Location** gp160 (599–606)  
**Author Location** gp41 (HAM112, O group)  
**Epitope** KGRLICYT  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* O group  
 HAM112 *HIV component:* gp160  
**Species (Isotype)** mouse (IgG2bκ)  
**References** Scheffel *et al.* 1999

- 105-732: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity – MAb 105-732 bound to two overlapping peptides. Scheffel *et al.* [1999]

No. 730

**MAb ID** 3D6 (IAM 41-3D6)  
**HXB2 Location** gp160 (599–613)  
**Author Location** gp41 (604–617 BH10)  
**Epitope** SGKLICTTAVPWNAS  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp41 cluster I, immunodominant region  
**Research Contact** H. Katinger, Inst. Appl. Microbiol., Vienna, Austria and Viral Testing Systems, Houston, TX  
**References** Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Cavacini *et al.* 1999; Cavacini *et al.* 1998a; Cavacini *et al.* 1998b; Kunert *et al.* 1998; Wisnewski *et al.* 1996; Stigler *et al.* 1995; Sattentau *et al.* 1995; Chen *et al.* 1994b; He *et al.* 1992; Felgenhauer *et al.* 1990

**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, kinetics, review, structure

- 3D6: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 3D6: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D, 3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cytoplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure, kinetics**)
- 3D6: Cavacini *et al.* note that both MAbs F223 and 3D6 are anti-HIV-1 Env MAbs that have an autoimmune response and that both use uses VH3 germline genes. Cavacini *et al.* [1999]
- 3D6: Binds to the immunodominant region of gp41 – a strong homology between heavy variable domains of hu MAb 3D6 and MAb F20 was observed, these MAbs may define a human Ab clonotype. Cavacini *et al.* [1998a] (**antibody sequence variable domain**)
- 3D6: The complete V, J and D(H) domain was sequenced – in contrast the sequences of five neutralizing MAbs, 3D6 had very little somatic mutation, with homologies of 97-98% relative to germline genes. Kunert *et al.* [1998] (**antibody sequence variable domain**)
- 3D6: 3D6 is V H3 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- 3D6: Called IAM 41-3D6: binding increased after pretreatment of infected cells with sCD4 – binding domain overlaps site that is critical for gp120-gp41 association. Sattentau *et al.* [1995] (**antibody binding site definition and exposure**)
- 3D6: Optimum peptide for binding 3D6 Fab was CSGKLICTTAVPW. Stigler *et al.* [1995] (**antibody binding site definition and exposure**)
- 3D6: This MAb binds to HIV gp41, and to a 43 kd protein found in human T, B and monocyte cell lines, proposed molecular mimicry. Chen *et al.* [1994b]
- 3D6: Fab fragment crystal structure. He *et al.* [1992] (**structure**)
- 3D6: Sequence of cDNA encoding V-regions. Felgenhauer *et al.* [1990] (**antibody sequence variable domain**)

No. 731

**MAb ID** F172-D8 (F172-D8, scFvD8)

**HXB2 Location** gp160 (604–615)

**Author Location** gp41 (609–620)

**Epitope** CTTAVPWNASWS?

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**References** Legastelois & Desgranges 2000

- F172-D8: As an approach to intercellular immunization using a single-chain variable fragment, scFvD8 was constructed based on the MAb F172-D8, directed at a loop in gp41 between the two heptad repeat regions – intracellular scFvD8 expression decreased gp160 expression and a scFvD8 transfected cell line did not support infection by HIV-1 Ba-L or primary isolates. Legastelois & Desgranges [2000]

**No.** 732

**MAb ID** D50

**HXB2 Location** gp160 (632–655)

**Author Location** gp41 (642–665)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* dimeric Env

**Species (Isotype)** mouse

**Ab Type** gp41 cluster II

**Research Contact** Patricia Earl and Christopher Broder, NIH

**References** Haynes & Montefiori 2006; de Rosny *et al.* 2004a; de Rosny *et al.* 2004b; Srivastava *et al.* 2002; Yang *et al.* 2000; Earl *et al.* 1997; Richardson *et al.* 1996; Binley *et al.* 1996; Earl *et al.* 1994

**Keywords** antibody binding site definition and exposure, antibody generation

- D50: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure**)
- D50: The MAb 2F5 binds to the C-heptad and is neutralizing, but the MAb D50 binds to the C-heptad and is not neutralizing. 2F5 binds preferentially to native gp41 prior to receptor activation. D50 prefers the triggered form after receptor activation. Trapped fusion-intermediates suggest 2F5 remains present shortly after gp120 triggering by CD4, but may be lost by the time the six-helix bundle is formed. D50 binds equally to the fusion-intermediate and six-helix bundle. 2F5 neutralization seems to block a later step of the fusion process. de Rosny *et al.* [2004b] (**antibody binding site definition and exposure**)
- D50: The mechanism of 2F5 neutralization was explored, and experiments suggest it is due to interference with a late step in viral entry. sCD4 binding to gp120 triggers conformational changes in gp41 allowing formation of the six helix bundle.

The NAb 2F5 preferentially bound native gp41, prior to receptor triggering, while the antibody D50 that also binds to the heptad region, near 2F5, is not neutralizing, and preferentially bound the CD4 triggered gp41. The C and N peptides that can be used to block the formation of the six helix bundle and lock gp41 in the fusion intermediate state after sCD4 triggering enabled 2F5 to bind after sCD4 triggering, while D50 was able to bind to both the peptide-trapped and sCD4 induced six helix bundle equally well, suggesting the D50 epitope is linear and more exposed after sCD4 binding. de Rosny *et al.* [2004a] (**antibody binding site definition and exposure**)

- D50: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – D50 was used to capture the o-gp140 for ELISA to test the antigenicity of o-gp140 using a panel of well characterized MAbs. Srivastava *et al.* [2002]
- D50: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – gp41 MAbs T4, D12, T3, and D50 bound less efficiently to gp140-GNC4 than did pooled sera, but T4 and D12 recognized the gp140-GNC4 trimer equivalently to gp140(-), and T3 and D50 recognized the trimer at greater levels than gp140(-). Yang *et al.* [2000] (**antibody binding site definition and exposure**)
- D50: Found to bind to a linear peptide, between Env amino acids 642-655 – can be blocked by the conformation dependent MAbs D16, D17, D31, D36, D37, D40, D44, D55, D59, T37, and T45 – the region is in the immunogenic cluster two region – reactive with 9/10 HIV-1 strains tested, all except HIV-1 ADA, in which the change E659D and E662A may result in the loss of binding (ELLE to DLLA). Earl *et al.* [1997] (**antibody binding site definition and exposure**)
- D50: Thought to be a discontinuous epitope recognizing residues between 649-668 – designated cluster II – Fabs D5, D11, G1, T3, M12, M15, S6, S8, S9, S10 block binding. Binley *et al.* [1996] (**antibody binding site definition and exposure**)
- D50: Richardson suggests this is a linear gp41 epitope. Richardson *et al.* [1996] (**antibody binding site definition and exposure**)
- D50: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

**No.** 733

**MAb ID** 5-21-3

**HXB2 Location** gp160 (642–665)

**Author Location** gp41 (642–665 HXB2)

**Epitope** IHSLIEESQNQQEKNEQELLELDK

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* gp41

**Species (Isotype)** mouse

**References** Scheffel *et al.* 1999; Hunt *et al.* 1990

- 5-21-3: Binds group M gp41, used as a control in a study of group O MAbs. Scheffel *et al.* [1999]
- 5-21-3: Recognizes a contiguous, conformation-dependent epitope in a hydrophilic region. Hunt *et al.* [1990]

**No.** 734  
**MAb ID** 120-16 (SZ-120.16)  
**HXB2 Location** gp160 (644–663)  
**Author Location** gp41 (644–663 HXB2)  
**Epitope** SLIEESQNQEKNEQELLEL  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG2κ)  
**References** Wisniewski *et al.* 1996; Forthal *et al.* 1995; Eddleston *et al.* 1993; Robinson *et al.* 1991; Xu *et al.* 1991; Tyler *et al.* 1990; Robinson *et al.* 1990b; Andris *et al.* 1992

- 120-16: 120-16 is V H4 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996]
- 120-16: No neutralizing activity, both ADCC and viral enhancing activity. Forthal *et al.* [1995]
- 120-16: Called SZ-120.16. Eddleston *et al.* [1993]
- 120-16: Synergizes with huMAb 50-69 *in vitro* to enhance HIV-1 infection. Robinson *et al.* [1991]
- 120-16: Less reactive region than AVERY region – most Abs involving this region bound conformational epitopes, this was the only linear one. Xu *et al.* [1991]
- 120-16: Antibody dependent enhancement (ADE) of HIV-1 IIIB infectivity, synergistically enhanced by MAb V10-9. Robinson *et al.* [1990b]
- 120-16: Potent ADCC (in contrast to MAb 98-43, gp41(579-604)). Tyler *et al.* [1990]

**No.** 735  
**MAb ID** 98-6 (SZ-98.6, 98.6, 98-6D)  
**HXB2 Location** gp160 (644–663)  
**Author Location** gp41 (644–663 HXB2)  
**Epitope** SLIEESQNQEKNEQELLEL  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG2κ)  
**Ab Type** gp41 alpha-helical hairpin intermediate, gp41 cluster II  
**Research Contact** Susan Zolla-Pazner (Zollas01@mccr6.med.nyu), NYU, NY  
**References** Holl *et al.* 2006a; Ling *et al.* 2004; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Follis *et al.* 2002; Golding *et al.* 2002b; Verrier *et al.* 2001; Taniguchi *et al.* 2000; Nyambi *et al.* 2000; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Nyambi *et al.* 1998; Hioe *et al.* 1997b; Wisniewski *et al.* 1996; Sattentau *et al.* 1995; Manca *et al.* 1995a; Forthal *et al.* 1995; Chen *et al.* 1995; Laal *et al.* 1994; Tani *et al.* 1994; Spear *et al.* 1993; Eddleston *et al.* 1993; Xu *et al.* 1991; Robinson *et al.* 1991; Sattentau & Moore 1991; Andris *et al.* 1992; Tyler *et al.* 1990; Robinson *et al.* 1990b; Till *et al.* 1989; Gorny *et al.* 1989; Pinter *et al.* 1989

**Keywords** ADCC, antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, binding affinity, complement, dendritic cells, enhancing activity, immunotoxin, kinetics, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 98-6: NIH AIDS Research and Reference Reagent Program: 1240.
- 98-6D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 98-6: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644–663); none have any neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 98-6: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. gp41 MAbs 246D, 98.6, 50-69, were decreased by trypsin, unaltered by thrombin, while NAb 2F5 binding was increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 98-6: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D, 3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cytoplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure, kinetics**)
- 98-6: Called 98-6D. Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 sensitivity is in-

- creased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- 98-6: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – 98-6 binds to a C-HR hairpin epitope and blocks fusion when added to a 2 hour E/T preincubation at 31.5 C, but if added after 1 hour, doesn't inhibit – this is in contrast to six-helix bundle Abs 167-D and 1281 that inhibit more efficiently when added after one hour of incubation. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)
  - 98-6: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6—six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D, while six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions, variant cross-recognition or cross-neutralization**)
  - 98-6: 98-6 and 2F5 both bind to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, and to C43 alone but not to N51 alone – 98-6 and 2F5 have comparable affinities for C43, but 98-6 has a higher affinity for the complex and the binding of 98-6 is not inhibited by N51. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure, binding affinity**)
  - 98-6: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
  - 98-6: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 cluster II anti-gp41 MAbs – of these 2F5, 167-D, 126-6, and 1281 bound across clades, but usually weakly, while 98-6 and 1342 had poor cross reactivity – Clade D isolates bound most consistently to cluster II MAbs – no neutralizing activity was observed when tested against 5 isolates, but 98-6 did not bind to these isolates. Nyambi *et al.* [2000] (**subtype comparisons**)
  - 98-6: The fusogenic form of gp41 is recognized by 98-6, and the epitope is a conformational epitope formed by the interaction of two regions of gp41 which form an alpha-helical bundle. Taniguchi *et al.* [2000] (**antibody binding site definition and exposure**)
  - 98-6: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – anti-gp41 Abs 98-6, 1367 and 1342 were not able to bind detectably with any of the viruses from any clade. Nyambi *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
  - 98-6: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
  - 98-6: 98-6 is V H4 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
  - 98-6: One of several anti-gp41 MAbs that bind to a gp41-maltose binding fusion protein designed to study the leucine zipper domain of gp41, showing that the construct has retained aspects of normal gp41 conformation. Chen *et al.* [1995] (**antibody binding site definition and exposure**)
  - 98-6: No neutralizing activity, positive ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC, enhancing activity**)
  - 98-6: Virions complexed to gp41 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
  - 98-6: Preferentially recognizes oligomeric form of gp41 – enhanced binding to HIV-1 infected cells at 37 degrees relative to 4 degrees – addition of sCD4 enhances binding. Sattentau *et al.* [1995] (**antibody binding site definition and exposure**)
  - 98-6: Epitope described as cluster II, 644-663, conformational – does not neutralize IIIB or synergize neutralization by anti-V3 MAb 447-52D or by CD4 BS MAbs. Laal *et al.* [1994] (**antibody binding site definition and exposure, antibody interactions, variant cross-recognition or cross-neutralization**)
  - 98-6: This MAb was expressed as a surface anti-gp41 monoclonal antibody receptor for gp41 on a CD4-negative B-cell line. Transfected cells could bind HIV Envelope, but could not be infected by HIV-1. When CD4 delivered by retroviral constructs was expressed on these cells, they acquired the ability to replicate HIV-1, and sIg/gp41 specifically enhanced viral replication. Tani *et al.* [1994]
  - 98-6: Called SZ-98.6 – binds to a conformational domain within aa 644-663 of gp41, and reacts with astrocytes, as do 167-7 and ND-15G1. Eddleston *et al.* [1993] (**antibody binding site definition and exposure**)
  - 98-6: Did not mediate deposition of complement component C3 on HIV infected cells, binding enhanced by sCD4. Spear *et al.* [1993] (**complement**)
  - 98-6: No neutralizing or enhancing activity. Robinson *et al.* [1991] (**enhancing activity**)
  - 98-6: Two fold increase in binding to gp120 in the presence of bound sCD4. Sattentau & Moore [1991] (**antibody binding site definition and exposure**)

- 98-6: Appeared to be specific for a conformational or discontinuous epitope. Xu *et al.* [1991] (**antibody binding site definition and exposure**)
- 98-6: No neutralizing or enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b] (**enhancing activity**)
- 98-6: Serves as target for antibody-dependent cellular cytotoxicity, ADCC. Tyler *et al.* [1990] (**ADCC**)
- 98-6: Kills HIV-infected cells when coupled to deglycosylated ricin A chain. Gorny *et al.* [1989] (**immunotoxin**)
- 98-6: Reacts preferentially with gp160 oligomer, compared to gp41 monomer. Pinter *et al.* [1989] (**antibody binding site definition and exposure**)
- 98-6: Toxic to HIV-infected T cells (H9) and monocytes (U937) when coupled to deglycosylated A chain of ricin. Till *et al.* [1989] (**immunotoxin**)

No. 736

**MAb ID** 167-7 (SZ-167.7)

**HXB2 Location** gp160 (644–663)

**Author Location** gp41 (644–663)

**Epitope** SLIEESQNQKKEQELLEL

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG2 $\lambda$ )

**Ab Type** gp41 cluster II

**References** Eddleston *et al.* 1993; Xu *et al.* 1991

- 167-7: Called SZ-167.7 – binds to a conformational domain within aa 644–663 of gp41, and reacts with astrocytes, as do 98-6 and ND-15G1. Eddleston *et al.* [1993]
- 167-7: Specific for a conformational epitope. Xu *et al.* [1991]

No. 737

**MAb ID** ND-15G1 (ND-15GI)

**HXB2 Location** gp160 (644–663)

**Author Location** gp41 (644–663 HXB2)

**Epitope** SLIEESQNQKKEQELLEL

**Subtype** B

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\kappa$ )

**Ab Type** gp41 cluster II

**References** Gorny & Zolla-Pazner 2004; Eddleston *et al.* 1993

**Keywords** antibody binding site definition and exposure, review

- ND-15G1: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644–663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- ND-15G1: Mapped to the conformational epitope within aa 644–663, and reacts with astrocytes, as do 98-6 and 167-7. Eddleston *et al.* [1993] (**antibody binding site definition and exposure**)

No. 738

**MAb ID** 167-D (167)

**HXB2 Location** gp160 (644–663)

**Author Location** gp41 (644–663 HXB2)

**Epitope** SLIEESQNQKKEQELLEL

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp41 cluster II, gp41 six-helix bundle

**Research Contact** Susan Zolla-Pazner (Zollas01@mcrcr6.med.nyu), NYU, NY

**References** Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Golding *et al.* 2002b; Nyambi *et al.* 2000; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Manca *et al.* 1995a; Forthal *et al.* 1995; Spear *et al.* 1993

**Keywords** ADCC, antibody binding site definition and exposure, complement, dendritic cells, enhancing activity, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 167-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 167-D: Called 167. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644–663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 167-D: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – 98-6 binds to a C-HR hairpin epitope and blocks fusion when added to a 2 hour E/T preincubation at 31.5 C, but if added after 1 hour, doesn't inhibit – this is in contrast to six-helix bundle Abs 167-D and 1281 that inhibit more efficiently when added after one hour of incubation. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)
- 167-D: This cluster II MAb binds to a conformational epitope in the region 644–663 – like most cluster II MAbs (126-6, 167-D, 1281, 1342, and 1379 all reacted similarly) it binds to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, but not to C43 nor to N51 alone. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 167-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 167-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 cluster II anti-gp41 MAbs – of these 2F5, 167-D, 126-6, and 1281 bound across clades, but usually weakly, while 98-6 and 1342 had poor cross reactivity – Clade D isolates bound most consistently to cluster II MAbs. Nyambi *et al.* [2000] (**subtype comparisons**)
- 167-D: No neutralizing activity, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC, enhancing activity, variant cross-recognition or cross-neutralization**)

- 167-D: Virions complexed to gp41 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
- 167-D: Did not mediate deposition of complement component C3 on HIV infected cells – complement mediated virolysis of MN and IIIB in the presence of sCD4. Spear *et al.* [1993] (**complement**)

**No.** 739

**MAb ID** polyclonal

**HXB2 Location** gp160 (659–670)

**Author Location** gp41 (659–670)

**Epitope** ELLELDKWASLW

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade *HIV component:* gp41 *Adjuvant:* QS21

**Species (Isotype)** guinea pig

**References** McGaughey *et al.* 2003

**Keywords** antibody binding site definition and exposure, binding affinity, vaccine antigen design

- 2F5: Cyclic peptides ELLELDKWASLW that adopt constrained beta-turn conformation of the 2F5 epitope beta-turn in the complexed crystal structure were synthesized and optimized 2F5 binding affinity. This peptide elicits high titer peptide-specific immune responses in guinea pigs that do not neutralize; the authors propose this may be the result of a short CDR3 loop in guinea pigs and additional recessed contact points between 2F5 and gp41. McGaughey *et al.* [2003] (**antibody binding site definition and exposure, vaccine antigen design, binding affinity**)

**No.** 740

**MAb ID** polyclonal

**HXB2 Location** gp160 (662–667)

**Author Location** gp41 (662–667)

**Epitope** ELDKWA

**Neutralizing** no

**Immunogen** vaccine

*HIV component:* gp41

**Species (Isotype)** guinea pig

**Ab Type** gp41 MPER (membrane proximal external region)

**References** Joyce *et al.* 2002

- 2F5: DP178 is a peptide derived from the C-term heptad repeat of gp41 that is a potent inhibitor of viral-mediated fusion – it contains ELDKWA but fails to stimulate 2F5-like NAb upon immunization – the peptide was extended to force an increase in helicity, and the modified peptide had a increase in affinity for 2F5, but upon guinea pig immunization although high peptide-specific Ab titers were achieved the sera were incapable of viral neutralization – the authors propose that 2F5 may be a low affinity maturation intermediate, which may account for its breadth and why it is hard to recreate the NAb response, but also suggests that the high concentrations required for neutralization are not relevant *in vivo*. Joyce *et al.* [2002]

**No.** 741

**MAb ID** polyclonal

**HXB2 Location** gp160 (662–667)

**Author Location** gp41

**Epitope** ELDKWA

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** mouse

**References** Liu *et al.* 2005b

**Keywords** vaccine antigen design, vaccine-specific epitope characteristics

- A peptide containing eight copies of the MAb 2F5's ELDKWA-epitope separated by aa spacers GSGGGGS, RS, and GS was used to test the impact of spacers on eliciting antibody responses to peptides. Both GSGGGGS and GS induced high titers of ELDKWA peptide-specific Abs in BALB/c mice, which reacted with rsgp41. Liu *et al.* [2005b] (**vaccine antigen design, vaccine-specific epitope characteristics**)

**No.** 742

**MAb ID** 5B2

**HXB2 Location** gp160 (662–667)

**Author Location** Env (669–674 IIIB)

**Epitope** ELDKWA

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide keyhole limpet hemocyanin (KLH) conjugate *Strain:* B clade IIIB *HIV component:* gp41

**Species (Isotype)** mouse (IgG)

**Ab Type** C-domain

**References** Tian *et al.* 2001

- 5B2: There is an RT specific Ab Szilvay *et al.* [1992] and a gp41 specific Ab Tian *et al.* [2001] both called 5B2. Tian *et al.* [2001]
- 5B2: Peptides GPGRIFY and ELDKWA were conjugated to keyhole limpet hemocyanin and used to raise mouse MAbs – MAb hybridomas were generated with defined specificity – 5B2 and 9G11 bind to the peptide and to rgp41. Tian *et al.* [2001]

**No.** 743

**MAb ID** 9G11

**HXB2 Location** gp160 (662–667)

**Author Location** Env (669–674 IIIB)

**Epitope** ELDKWA

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide keyhole limpet hemocyanin (KLH) conjugate *Strain:* B clade IIIB *HIV component:* gp41

**Species (Isotype)** mouse (IgG)

**Ab Type** C-domain

**References** Tian *et al.* 2001

- 9G11: Peptides GPGRIFY and ELDKWA were conjugated to KLH and used to raise mouse monoclonal Ab—MAb hybridomas were generated with defined specificity—5B2 and 9G11 bind to the peptide and to rgp41. Tian *et al.* [2001]



**No.** 744  
**MAb ID** TH-Ab1  
**HXB2 Location** gp160 (662–667)  
**Author Location** gp41 (669–674)  
**Epitope** ELNKWA  
**Neutralizing** L P  
**Immunogen** vaccine  
*Vector/Type:* peptide keyhole limpet hemocyanin (KLH) conjugate *Strain:* B clade TH936705 *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** rabbit (IgG1)  
**Ab Type** C-domain  
**References** Dong *et al.* 2001; Xiao *et al.* 2000a

- TH-Ab1: ELNKWA is an escape variant not recognized by the broadly neutralizing MAb 2F5, which recognizes the core epitope ELDKWA—Abs were raised against the peptide escape variant CGELNKWAGELNKWA linked to KLH carrier—these polyclonal antibodies, like the MAb TH-Ab1 also raised to ELNKWA, could recognize ELDKWA and escape mutant peptide epitopes ELEKWA and ELDEWA. Dong *et al.* [2001]

**No.** 745  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (662–667)  
**Author Location** gp41  
**Epitope** ELDKWA  
**Neutralizing** L P  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* gp41

**Species (Isotype)** rabbit  
**Ab Type** C-domain  
**References** Liao *et al.* 2000

- Low levels of anti-ELDKWA antibodies are observed in HIV-1 + individuals, so a C-domain P2 peptide linked to a carrier was used to immunize mice and rabbits, and stimulated a high-level anti-ELDKWA response in mice and rabbits – vaccine was C-TSLIHSLLIEESQNQQEKNEQELLELDKWA linked to carrier peptide K/G [(KGGG)<sub>7</sub>-K]. Liao *et al.* [2000]

**No.** 746  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (662–667)  
**Author Location** gp41 (669–674)  
**Epitope** ELDKWA  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* Env *Adjuvant:* BSA

**Species (Isotype)** rabbit, mouse  
**Ab Type** C-domain, gp41 MPER (membrane proximal external region)  
**References** Xiao *et al.* 2000b

- Strong epitope-specific neutralizing antibody responses were induced using a Env peptide bound to BSA, C(ELDKWAG)<sub>4</sub>-BSA, but not full gp160. Xiao *et al.* [2000b]

**No.** 747  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (662–667)  
**Author Location** gp41 (662–667 BH10)  
**Epitope** ELDKWA  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* influenza *Strain:* B clade BH10 *HIV component:* gp41

**Species (Isotype)** mouse (IgA, IgG)  
**Ab Type** C-domain  
**References** Muster *et al.* 1995; Muster *et al.* 1994

- Sustained ELDKWA specific IgA response in mucosa of immunized mice. Muster *et al.* [1995]

**No.** 748  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (662–667)  
**Author Location** gp120 (669–674)  
**Epitope** ELDKWA  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein, polyepitope *HIV component:* gp160 *Adjuvant:* BSA

**Species (Isotype)** rabbit  
**Ab Type** C-domain  
**References** Lu *et al.* 2000b; Lu *et al.* 2000c

- High titer response to ELDKWA and RILAVERYLKD was observed upon vaccination with multiple-epitope vaccine CG-GPGRIFY-G-ELDKWA-G-RILAVERYLKD conjugated to BSA, with a weak response to GPGRIFY – immunization with CG-(ELDKWA-GPGRIFY)<sub>2</sub>-K was also tried, yielding a strong Ab response to both ELDKWA and GPGRIFY – gp160 vaccination yielded strong Ab response but not to any of the peptides studied here. Lu *et al.* [2000c,b]

**No.** 749  
**MAb ID** 14D9  
**HXB2 Location** gp160 (662–667)  
**Author Location** gp41 (669–674 MVP5180)  
**Epitope** ELDEWA  
**Subtype** B, CRF01\_AE, O  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide keyhole limpet hemocyanin (KLH) conjugate *Strain:* natural variants *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp41 adjacent to cluster II, C-term, gp41 MPER (membrane proximal external region)  
**References** Huang *et al.* 2002  
**Keywords** antibody binding site definition and exposure, antibody generation, subtype comparisons, variant cross-recognition or cross-neutralization

- 14D9: This mouse MAb was raised against a variant of EL-DKWA core epitope of the NAb 2F5, eldEwa, derived from the 2F5 neutralization resistance variant MVP5180. The eldEwa peptide was conjugated to the carrier protein keyhole limpet hemocyanin (KLH) and administered to BALB/c mice and 14D9 was prepared using standard hybridoma methods. 2F5 does not bind to the variants eldEwa, elNkwa (B.TH.TH936705) or elEkwa, while 14D9 binds only to eldEwa and not ELDKWA. The eldEwa variant is common in the HIV-1 O group. Huang *et al.* [2002] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 750

**MAb ID** 2F5 (IAM 2F5, IAM-41-2F5, IAM2F5, c2F5)

**HXB2 Location** gp160 (662–667)

**Author Location** gp41 (662–667 BH10)

**Epitope** ELDKWA

**Neutralizing** L P

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG3κ)

**Ab Type** gp41 adjacent to cluster II, C-term, gp41 MPER (membrane proximal external region)

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**References** Gray *et al.* 2006; Joos *et al.* 2006; Braibant *et al.* 2006; Davis *et al.* 2006; Cham *et al.* 2006; Choudhry *et al.* 2006; Holl *et al.* 2006a; Jiang *et al.* 2006; Herrera *et al.* 2006; Sack *et al.* 2007; Quakkelaar *et al.* 2007; Nelson *et al.* 2007; Law *et al.* 2007; Kraft *et al.* 2007; Huang *et al.* 2007a; Haim *et al.* 2007; Dhillon *et al.* 2007; Kothe *et al.* 2007; Ferrantelli *et al.* 2007; Dimitrov *et al.* 2007; Dey *et al.* 2007; Choudhry *et al.* 2007; Blish *et al.* 2007; Alam *et al.* 2007; Liao *et al.* 2006; Holl *et al.* 2006b; Haynes & Montefiori 2006; Dong & Chen 2006; Alving *et al.* 2006; Zwick *et al.* 2005; Wang *et al.* 2005; Srisurapanon *et al.* 2005; Ren *et al.* 2005; Pinter *et al.* 2005; Nakowitsch *et al.* 2005; Lusso *et al.* 2005; Luo *et al.* 2006; Louis *et al.* 2005; Liu *et al.* 2005b; Krachmarov *et al.* 2005; Ho *et al.* 2005; Haynes *et al.* 2005; Chakrabarti *et al.* 2005; Dong *et al.* 2005; Biron *et al.* 2005; Zwick *et al.* 2004; Menendez *et al.* 2004; Safrit *et al.* 2004; Pugach *et al.* 2004; Pinter *et al.* 2004; Opalka *et al.* 2004; Nabatov *et al.* 2004; McCaffrey *et al.* 2004; Lorin *et al.* 2004; Ling *et al.* 2004; Liao *et al.* 2004; Jeffs *et al.* 2004; Ferrantelli *et al.* 2004a; Ferrantelli *et al.* 2004b; de Rosny *et al.* 2004a; de Rosny *et al.* 2004b; Binley *et al.* 2004; Gorny & Zolla-Pazner 2004; Wolbank *et al.* 2003; Ohagen *et al.* 2003; Montefiori *et al.* 2003; McGaughey *et al.* 2003; Mascola *et al.* 2003; Kitabwalla *et al.* 2003; Wang 2003;

Richman *et al.* 2003; Mascola 2003; Hart *et al.* 2003; Ferrantelli *et al.* 2003; Dey *et al.* 2003; Binley *et al.* 2003; Stiegler *et al.* 2002; Li *et al.* 2002; Huang *et al.* 2002; Gorry *et al.* 2002; Finnegan *et al.* 2002; Follis *et al.* 2002; Cavacini *et al.* 2002; Bures *et al.* 2002; Liu *et al.* 2002; Ferrantelli & Ruprecht 2002; Zhang *et al.* 2002; Kunert *et al.* 2002; Mascola 2002; Grundner *et al.* 2002; Xiang *et al.* 2002b; Clerici *et al.* 2002a; Joyce *et al.* 2002; Chakrabarti *et al.* 2002; Xu *et al.* 2002; Ho *et al.* 2002; Tian *et al.* 2002; Schulke *et al.* 2002; Golding *et al.* 2002b; Srivastava *et al.* 2002; Armbruster *et al.* 2002; Root *et al.* 2001; Xu *et al.* 2001; Hofmann-Lehmann *et al.* 2001; Stiegler *et al.* 2001; Verrier *et al.* 2001; Spenlehauer *et al.* 2001; Parker *et al.* 2001; Zeder-Lutz *et al.* 2001; Moore *et al.* 2001; Barnett *et al.* 2001; Mascola & Nabel 2001; Zwick *et al.* 2001c; Zwick *et al.* 2001b; York *et al.* 2001; Tumanova *et al.* 2001; Kolchinsky *et al.* 2001; Dong *et al.* 2001; Si *et al.* 2001; Yang *et al.* 2000; Xiao *et al.* 2000c; Coeffier *et al.* 2000; Sanhadji *et al.* 2000; Pai *et al.* 2002; Park *et al.* 2000; Nyambi *et al.* 2000; Lu *et al.* 2000b; Lu *et al.* 2000c; Liao *et al.* 2000; Kunert *et al.* 2000; Gorny & Zolla-Pazner 2000; Robert-Guroff 2000; Baba *et al.* 2000; Mascola *et al.* 2000; Mascola *et al.* 1999; Parren *et al.* 1999; Muhlbacher *et al.* 1999; Beddows *et al.* 1999; Poignard *et al.* 1999; Montefiori & Evans 1999; Frankel *et al.* 1998; Kunert *et al.* 1998; Geffin *et al.* 1998; Parren *et al.* 1998b; Jiang *et al.* 1998; Li *et al.* 1998; Takefman *et al.* 1998; Ernst *et al.* 1998; Fouts *et al.* 1998; Trkola *et al.* 1998; Yang *et al.* 1998; Parren *et al.* 1998a; Connor *et al.* 1998; Mondor *et al.* 1998; Andrus *et al.* 1998; Gorny *et al.* 1997; Earl *et al.* 1997; Burton & Montefiori 1997; Ugolini *et al.* 1997; Turbica *et al.* 1997; Stamatos *et al.* 1997; Mascola *et al.* 1997; Moore & Trkola 1997; Kessler II *et al.* 1997; Li *et al.* 1997; Mo *et al.* 1997; D'Souza *et al.* 1997; Schutten *et al.* 1997; Purtscher *et al.* 1996; Stoiber *et al.* 1996; McKeating *et al.* 1996; Pincus *et al.* 1996; Conley *et al.* 1996; Sattentau 1996; Poignard *et al.* 1996b; McKeating 1996; Calarota *et al.* 1996; Kessler *et al.* 1995; Neurath *et al.* 1995; Moore & Ho 1995; Sattentau *et al.* 1995; Trkola *et al.* 1995; D'Souza *et al.* 1995; Beretta & Dalglish 1994; Muster *et al.* 1994; McGaughey *et al.* 2004; Chen *et al.* 1994b; Thali *et al.* 1994; Conley *et al.* 1994b; D'Souza *et al.* 1994; Dacheux *et al.* 2004; Buchacher *et al.* 1994; Laal *et al.* 1994; Purtscher *et al.* 1994; Klasse *et al.* 1993a; Allaway *et al.* 1993;

Muster *et al.* 1993; Buchacher *et al.* 1992

**Keywords** acute/early infection, adjuvant comparison, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, autologous responses, binding affinity, brain/CSF, co-receptor, complement, dendritic cells, enhancing activity, escape, HIV exposed persistently seronegative (HEPS), immunoprophylaxis, immunotherapy, immunotoxin, isotype switch, kinetics, mimotopes, mother-to-infant transmission, mucosal immunity, neutralization, optimal epitope, rate of progression, responses in children, review, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization, viral fitness and reversion

- 2F5: UK Medical Research Council AIDS reagent: ARP3063.
- 2F5: NIH AIDS Research and Reference Reagent Program: 1475.
- 2F5: The autoantibody nature of the two membrane proximal HIV-1 neutralizing antibodies, 2F5 and 4E10, was evaluated by comparison to human anti-cardiolipin MAbs derived from a primary antiphospholipid syndrome patient. Both 2F5 and 4E10 bound specifically to cardiolipin. CDR3 sequence similarities between 2F5, 4E10 and anti-cardiolipin MAbs were observed. Both 2F5 and 4E10 binding to the peptide-lipid conjugate was best fit by a two-step conformational change model. These results suggest that these MAbs share binding and structural similarities with human autoantibodies and their induction by vaccines or natural infection therefore might be limited by immune tolerance mechanisms. Alam *et al.* [2007] (**antibody sequence variable domain**)
- 2F5: 7/15 and 9/15 subtype A HIV-1 envelopes from samples taken early in infection were neutralized by MAbs 4E10 and 2F5, respectively, and the potency was generally modest. Mutational patterns in the MAb binding sites did not readily explain the observed patterns of sensitivity and resistance. Blish *et al.* [2007] (**neutralization, variant cross-recognition or cross-neutralization, acute/early infection, subtype comparisons**)
- 2F5: 2F5, 4E10, and m46 neutralization was more potent when tested in a HeLa cell line expressing low CCR5 than in a HeLa cell line expressing high CCR5 levels. PBMC tend to have low CCR5 expression. Choudhry *et al.* [2007] (**neutralization, assay standardization/improvement**)
- 2F5: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP trimers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. Dey *et al.* [2007] (**vaccine antigen design**)
- 2F5: Chimeric SIV viruses containing 2F5 and 4E10 epitopes were not neutralized by broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals, indicating that MPER NAb epitopes did not account for the broad neutralizing activity observed. Dhillon *et al.* [2007] (**antibody binding site definition and exposure, neutralization**)
- 2F5: Kinetics experiments of 2F5 binding to MPER region during viral fusion showed that the 2F5 kinetics resembled those of the six-helix bundle formation and fusion blocker C34, indicating that the function of MPER in the fusion cascade is still in effect at a late stage in the fusion reaction. Binding of 2F5 was shown to decrease upon triggering HIV-1 Env-expressing cells with appropriate target cells and addition of C34 did not counteract this loss, suggesting that changes in exposure of MPER occur independently of the six-helix bundle formation. Dimitrov *et al.* [2007] (**antibody binding site definition and exposure, neutralization, kinetics, binding affinity**)
- 2F5: Newborn macaques were challenged orally with the highly pathogenic SHIV89.6P and then treated intravenously with a combination of IgG1b12, 2G12, 2F5 and 4E10 one and 12 hours post-virus exposure. All control animals became highly viremic and developed AIDS. In the group treated with mAbs 1 hour post-virus exposure, 3/4 animals were protected from persistent systemic infection and one was protected from disease. In the group treated with mAbs 12 hour post-virus exposure, one animal was protected from persistent systemic infection and disease was prevented or delayed in two animals. IgG1b12, 2G12, and 4E10 were also given 24 hours after exposure in a separate study; 4/4 treated animals become viremic, but with delayed and lower peak viremia relative to controls. 3/4 treated animals did not get AIDS during the follow up period, and 1 showed a delayed progression to AIDS, while the 4 untreated animals died of AIDS. Thus the success of passive immunization with NAb depends on the time window between virus exposure and the start of immunoprophylaxis. Ferrantelli *et al.* [2007] (**immunoprophylaxis**)
- 2F5: Using synchronously infected cell cultures, the binding of b12, 2F5 and 2G12 to the cell-free virus interferes with a step of infection subsequent to cell attachment. HIV escape from b12 occurred 30 and 10 min before escape from 2F5 for IIIB infection of HeLa cells and JRFL infection of Cf2Th-CD4/CCR5 cells, respectively, indicating that neutralization efficiency is determined by the time frames during which Ab can bind to the receptor-activated envelope proteins during the entry phase. 2F5 neutralization was enhanced by a decreasing the rate of coreceptor CXCR4 engagement, presumably by increasing the time the CD4 bound Env was available and slowing viral entry kinetics. Haim *et al.* [2007] (**kinetics**)
- 2F5: Binding of 2F5 to gp41 was not significantly affected by the small molecule HIV-1 entry inhibitor IC9564. IC9564 induces conformational change of gp120 to allow CD4i antibody 17b to bind, but inhibits CD4-induced gp41 conformational changes. Huang *et al.* [2007a]

- 2F5: Four consensus B Env constructs: full length gp160, un-cleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective un-cleaved version mediated infection using the CCR5 co-receptor. Primary isolate Envs varied between completely resistant or somewhat sensitive to neutralization by membrane proximal Nabs 4E10 and 2F5. The most sensitive Con B construct was the truncated version of Con B Env with a stop codon immediately following the membrane spanning domain, suggesting that truncation of the gp41 cytoplasmic domain facilitates greater accessibility of the MPER region. The Con B gp160 was quite resistant, and the gp160-201N/S more sensitive, to 4E10 and 2F5. Kothe *et al.* [2007] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)
- 2F5: Viruses from 304 days and at 643 days (time of death) post-infection of a macaque infected with SHIV SF162P4 were resistant to contemporaneous serum that had broadly reactive NAbs. While resistance to anti-V3, b12, and anti-V1 MABs developed over time, viruses remained sensitive to 2F5 and 2G12. Kraft *et al.* [2007] (**neutralization, escape**)
- 2F5: High levels of gp120-specific Abs were elicited when mice and rabbits were immunized by DNA priming and protein boosting with G1 and G2 grafts, consisting of 2F5 and 4E10, and 4E10 epitopes, respectively, engrafted into the V1/V2 region of gp120. A consistent NAb response against the homologous JR-FL virus was detected in rabbits but not in mice. 4E10 bound to the engrafted construct, but embedding the MPER epitopes in the immunogenic V1/V2 region did not result in eliciting anti-MPER antibodies in mice or rabbits. 2F5 bound to the Graft1 antigen consisting of 2F5 and 4E10 epitopes engrafted into the immunogenic V1/V2 region of gp120 much more weakly than to gp41 suggesting that the 2F5 epitope might be hidden or folded incorrectly in this construct. Law *et al.* [2007] (**vaccine antigen design**)
- 2F5: Z13e1, a high affinity variant of Fab Z13, was identified through targeted mutagenesis and affinity selection against gp41 and an MPER peptide. Z13e1 showed 100-fold improvement in binding affinity for MPER antigens over Z13, but was still less potent than 4E10 at neutralizing several pseudotyped Envs. Neutralization assays of HIV-1 JR2 MPER alanine mutants showed that mutants W666A and W672A were completely resistant to neutralization by 2F5. Nelson *et al.* [2007] (**antibody binding site definition and exposure**)
- 2F5: This study found that, contrary to expectations, the viruses resistant to b12, 4E10, 2G12 and 2F5 neutralization did not have lower replication kinetics than viruses sensitive to neutralization. Viruses from early infection tended to have relatively low replication rates. Quakkelaar *et al.* [2007] (**viral fitness and reversion, escape**)
- 2F5: 2F5 was produced in transgenic tobacco BY2 suspension cell cultures. The plant derived antibody was efficiently assembled and intact. When compared to CHO-derived 2F5, the plant derived 2F5 showed similar kinetic properties and 89% of the binding capacity of the CHO-derived Ab. However, it was only 33% as efficient in HIV-1 RF neutralization assay. Sack *et al.* [2007] (**neutralization, binding affinity**)
- 2F5: This review summarizes current knowledge of HIV-1 lipid-protein interactions and antibodies to liposomal phospholipids and cholesterol. A potential use of Abs to lipids to neutralize HIV-1 and a potential role of the broadly neutralizing HIV-1 Abs, mainly 2F5 and 4E10, in binding to phospholipids is discussed. Alving *et al.* [2006] (**antibody binding site definition and exposure, neutralization, review**)
- 2F5: Inhibition of 2F5 binding to gp160 by 2F5-like Abs in sera from long-term non-progressors (LTNP) was determined. 2F5-like Abs were present in almost all sera from LTNPs but at a lower levels than b12. No statistically significant correlation was found for the specificity of this Ab comparing sera able to neutralize all four HIV-1 strains and sera that could not. Braibant *et al.* [2006] (**enhancing activity, neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 2F5: The majority of broadly cross-reactive neutralizing (BCN) Envs were neutralized at lower concentrations of 2F5 than the non-BCN Envs. Amino acid variability of the 2F5 epitope was examined. The presence of T at position 662 was associated with increased sensitivity to neutralization by 2F5 while the K665N mutation resulted in resistance to 2F5 Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, escape, subtype comparisons**)
- 2F5: Neutralization of HIV-1 primary isolates of different HIV-1 clades (A, B, C, D, E) by 2F5 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of 2F5 in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor, neutralization, variant cross-recognition or cross-neutralization**)
- 2F5: Neutralization rates and rate constants for the neutralization of clade B primary isolates SF33, SF162 and 89.6 by this Ab were determined. Statistically significant neutralization was not observed for isolates SF162 and 89.6. It was shown that neutralization sensitivity is not associated with neutralization of cell-associated or free virus. Davis *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, kinetics**)
- 2F5: Genetic variability and co-variation of the mAb 2F5, 4E10 and Z13 epitopes in B and non B clades was investigated. A significant shift in the predominant sequence patterns over time was observed for all three epitopes. Also, significant inter-subtype genetic variability of the three epitopes was detected. However, the 4E10 epitope displayed a more similar variability within B clade and non-B clades, concurring with the cross-clade neutralizing activity of this mAb. Epitope co-variation was also noted, as one third of the recently isolated HIV-1 strains displayed simultaneous epitope variants. Dong & Chen [2006] (**antibody binding site definition and exposure, subtype comparisons**)
- 2F5: Env-pseudotyped viruses were constructed from the gp160 envelope genes from seven children infected with subtype C HIV-1. 2F5 failed to neutralize any of the seven viruses, correlating with the replacement of the crucial lysine at the position 665 of the 2F5 epitope on these viruses. When this Ab was mixed with IgG1b12 and 2G12, the neutralization was similar as to IgG1b12 alone, indicating that the majority of the pool activity was due to IgG1b12. When

- 4E10 was added to this mix, all isolates were neutralized. Gray *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, responses in children, mother-to-infant transmission**)
- 2F5: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure, neutralization, optimal epitope, escape, review, subtype comparisons, structure**)
  - 2F5: Viruses with cleavage-competent 2G12-knockout Env and cleavage-defective Env able to bind 2G12 were constructed. 2F5 was shown to bind more to the cleavage-defective Envs than to the cleavage-competent Envs. More 2F5 binding was detected to cells co-expressing wildtype and cleavage-defective Env than to a mixture of cells expressing either, suggesting that uncleaved Env proteins have an enhancing effect of the binding of 2F5 to the heterotrimer or that fewer than three Abs can bind per trimer and that 2F5 has a higher affinity for the uncleaved Env. Env pseudotyped virions bearing either Wt3.2P(+)/gp140 $\delta$ ct Env or a mixture of the wildtype and cleavage-defective Env had similar sensitivities to neutralization by 2F5. Herrera *et al.* [2006] (**neutralization, binding affinity**)
  - 2F5: Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in iMDDCs was evaluated. The neutralizing activity of 2F5 was observed to be higher in iMDDCs than in PBLs and PHA-stimulated PBMCs. Furthermore, the kinetics of Ab addition showed that this mAb interfered with the first events of HIV-1 entry in iMDDCs. High concentrations of 2F5 triggered a non-HIV-related maturation of target cells. Blockade of Fc $\gamma$ RII on iMDDCs decreased the anti-HIV activity of 2F5 while increased expression of Fc $\gamma$ RI increased inhibition of HIV by 2F5, suggesting the involvement of these receptors in the HIV-inhibitory activity of this Ab. Holl *et al.* [2006b] (**neutralization, kinetics, dendritic cells**)
  - 2F5: The ability of this Ab to inhibit viral growth was increased when macrophages and immature dendritic cells (iDCs) were used as target cells instead of PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-Fc $\gamma$ R-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**dendritic cells**)
  - 2F5: 2F5 was shown to interact with cells transiently transfected by VSV-gp120 expressing vector and stained with sera from mice immunized intranasally with VSV vector expressing HIV-1 HXB2 gp120, indicating that VSV-HXB2 immunization produced anti-HIV-1 Abs. Jiang *et al.* [2006] (**vaccine antigen design**)
  - 2F5: Pharmacokinetic properties of this Ab were studied in HIV infected patients infused with high doses of 2G12. The Ab did not elicit an endogenous immune response and had distribution and systemic clearance values similar to other Abs. The elimination half-life was measured to 4.3 days. Joos *et al.* [2006] (**kinetics, immunotherapy**)
  - 2F5: The gp140 $\delta$ CFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. 2F5 was shown to bind specifically to CON6, CON-S and subtype B recombinant proteins but not to subtype A and C recombinant proteins or to the two subtype B gp120 proteins. The specific binding of 2F5 to CON-S indicated that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure, vaccine antigen design, subtype comparisons**)
  - 2F5: gp41 and p15E of the porcine endogenous retrovirus (PERV) share structural and functional similarities, and epitopes in the membrane proximal region of p15E are able to elicit NAbs upon immunization with soluble p15E. Rabbits immunized with a VSV recombinant expressing an HIV-1 membrane-proximal external region (MPER) fused to PERV p15E, with a fusion p15E-HIV MPER protein boost, elicited HIV specific NAbs. The MPER contains the 2F5 epitope, and the 2F5 MAb was used as a positive control for neutralization in this study, and could bind to the vaccine construct. Luo *et al.* [2006] (**vaccine antigen design**)
  - 2F5: Circular dichroism and NMR were used to analyze the structure of the HIV-1 inhibitor peptide T-20 (gp41 HXB2 aa 638-673) that contains the full 2F5 and partial 4E10 epitope. T-20 was unstructured towards the N terminus, and helical in the central and C-terminal regions. The 2F5 epitope sequence (gp41 HXB2 657-670) forms an intrinsic helical structure, which is stable in water. Biron *et al.* [2005] (**structure**)
  - 2F5: Guinea pigs were immunized with a hybrid HXB2/BaL Env (HIV HXB/BaL gp140 $\delta$ CFI, clade B) in which the tip of the V3 loop (GPGRA) was replaced with the 2F5 epitope LELDKWAS. 2F5 bound to the Env that carried the V3-replacement 2F5 epitope, but antibodies against this construct only neutralized the X4-tropic lab adapted HIV strain IIIB, and not CCR5-HIV BaL or SF162 isolates. Chakrabarti *et al.* [2005] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)
  - 2F5: 2F5 recognizes the epitope ELDKWA, but does not neutralize viruses carrying the commonly found mutated epitope variants: ELDeWA, ELDSWA, ELDNWA, ELDQWA, ELDTWA, or ELNkWA. Peptide cocktails containing ELDKWA, ELNkWA, ELDeWk, and ELkWA elicit polyclonal antibodies in rabbits that can bind to all of the natural variants that are escape variants for 2F5 expressed in gp41 via Western blotting, as well as ELDrWA. Dong *et al.* [2005] (**vaccine antigen design, variant cross-recognition or cross-neutralization, escape**)
  - 2F5: 2F5 and 4E10 both bind to membrane proximal regions of gp41, and have long hydrophobic CDR3 regions characteristic of polyspecific autoreactive antibodies. Of 35 Env-specific MAbs tested, only 2F5 and 4E10 were reactive with phospholipid cardiolipin. Vaccine induction of antibodies that react with these gp41 membrane proximal regions may be rare because of elimination due to autoantigen mimicry. 2F5 also reacted with centromere B and histone autoantigens, and both

4E10 and 2F5 reacted with HEp-2 cells with diffuse cytoplasmic and nuclear patterns indicating polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

- 2F5: In an attempt to elicit 2F5-like antibodies, the 2F5 epitope ELDKWAS was constrained in the beta-turn sites of the immunoglobulin heavy chain, or alternatively was attached at the C-terminal ends of the immunoglobulin light chain. The constrained heavy chain inserted epitopes bound to 2F5 with 10-fold higher affinity than the light chain unconstrained versions, and when used as an immunogen, elicited epitope-specific antibodies in rabbits, but these antibodies could not neutralize the virus. Ho *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- 2F5: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Neutralization by Cameroonian sera MAbs was blocked by Clade A and B V3 loop fusion proteins, while NAbs to non-V3 epitopes, 2F5, 2G12, and b12, were not blocked. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 2F5: A peptide containing eight copies of the ELDKWA-epitope separated by aa spacers GSGGGGS, RS, and GS was used to test the impact of spacers on eliciting antibody responses to peptides. Both GSGGGGS and GS induced high titers of ELDKWA peptide-specific Abs in BALB/c mice, which reacted with rsgp41. 2F5 served as a positive control in a Western Blot to determine whether epitope-specific Abs bound to recombinant protein rsgp41. Liu *et al.* [2005b] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- 2F5: Nine anti-gp41 bivalent Fabs that interacted with either or both of the 6-helix bundle and the internal coiled-coil of N-helices of gp41 were selected from a non-immune human phage display library. The IC50 range for the inhibition of LAV ENV-mediated cell-fusion was 6-61 ug/ml. For context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here. Louis *et al.* [2005] (**neutralization**)
- 2F5: Passive immunization of 8 HIV-1 infected patients with 4E10, 2F5 and 2G12 (day 0, 4E10; days 7, 14 and 21 4E10+2G12+2F5; virus isolated on days 0 and 77) resulted in 0/8 patients with virus that escaped all three NAbs. No viruses fully escaped 2F5, although 5/8 developed a more than 2-fold increase in 2F5 IC50 concentrations at day 77. No changes in the 2F5 epitope were observed in the 77 day study period, although 3 patients had unusual 2F5 epitope sequences to start with (not A/ELDKWA but SLNNWN, ALDTWE, or KFD-NWA); all viruses were susceptible to 2F5 neutralization, although to varying degrees. In a companion in vitro study, resistance to a single MAB emerged in 3-22 weeks, but triple combination resistance was slower and characterized by decreased viral fitness. In the core of the 2F5 epitope, LDKW,

the L and W were completely conserved in the in vitro study, but 9/13 cases had a D->N change, 1/13 a K->N, and 1/13 a K->Q. The lack of resistance to the combination of MAbs in vivo and the reduced fitness of the escape mutants selected in vitro suggests passive immunotherapy may be of value in HIV infection. Nakowitsch *et al.* [2005] (**escape, immunotherapy**)

- 2F5: This study is about the V2 MAB C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potentially neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MAbs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAB 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
- 2F5: The antibody M2 is specific for a peptide flag inserted into the V4 loop of YU-2, a neutralization resistant variant with a short V4 loop. IgG1b12 and 2F5 could neutralize both the WT YU-2 and the modified variant. The high diversity of V4 suggests it does not play a direct role in receptor binding or viral entry, yet M2, specific for the peptide insert tag, can neutralize the modified virus, demonstrating that neutralizing activity doesn't have to block functionality of the virus. Ren *et al.* [2005] (**neutralization**)
- 2F5: Ab titers to the 2F5 binding peptide ELDKWA were tested by peptide ELISA in sera from Thais infected with CRF01 virus who were asymptomatic versus those who had AIDS, and antibody titers were found to be significantly lower in AIDS patients. The frequency of recognition of this peptide was low overall (15-35%) in CRF01 infections, as well as infections with clades A-G. Srisurapanon *et al.* [2005] (**variant cross-recognition or cross-neutralization, subtype comparisons, rate of progression**)
- 2F5: A multi-epitope ELDKWA/ELDEWA string in a glutathione S-transferase (GST) backbone elicited Abs in mice and rabbits that could bind to gp41 carrying either the 2F5 susceptible ELDKWA variant, or the ELDEWA escape variant. Vaccinations with only the ELDKWA epitope or the ELDEWA embedded-peptide constructs yielded type specific Abs. Wang *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics, escape**)
- 2F5: Alanine scanning mutations of the 21 amino acid region between positions 660-680 showed that only Ala substitutions in the DKW at the core of the epitope reduced binding, positions lleLDKWanlwnwfdisnwlw. No single Ala mutation was resistant to both 2F4 and 4E10. Ala substitutions in 12 of the 20 positions enhanced neutralization sensitivity, LLeLdkwanLWNWfdIsnWLW. 2F5 inhibits the neutralization activity of peptide T20. Zwick *et al.* [2005] (**antibody binding site definition and exposure, escape**)
- 2F5: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. 2F5 was cross-reactive with A, B, and E subtype viruses, some D, and no C clade viruses. DKW was defined as the core motif, and was found in only 25% of C clade sequences in the database. It was found in C clade viruses in a country specific manner – common in Burundi, Brazil and Ethiopia, rare in Botswana, India, and S. Africa. The potency of the neu-

- tralizing activity was somewhat context-dependent. DQW is a common D clade variant from Uganda, and all D viruses in this study were Ugandan. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- 2F5: Env sequences were derived from 4 men at primary infection and four years later; the antigenicity in terms of the ability to bind to 2G12, 2F5 and IgG1b12 was determined. 2G12 bound primarily to late clones in 3 of the 4 patients, and to both early and late in the other patient. Neither 2F5 nor IgG1b12 showed a difference in binding affinity to early or late envelopes. Dacheux *et al.* [2004] (**antibody binding site definition and exposure, acute/early infection, kinetics**)
  - 2F5: Neonatal rhesus macaques were exposed orally to a pathogenic SHIV, 89.6P. 4/8 were given an intramuscular, passive immunization consisting of NAb 2G12, 2F5 and 4E10, each given at a different body sites at 40 mg/kg per Ab, at one hour and again at 8 days after exposure to 89.6P. The four animals that were untreated all died with a mean survival time of 5.5 weeks, the four animals that got the NAb combination were protected from infection. This model suggests antibodies may be protective against mother-to-infant transmission of HIV. Ferrantelli *et al.* [2004b] (**mother-to-infant transmission**)
  - 2F5: Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. IgG1b12 could neutralize some O group strains when used on its own, and quadruple combination of b12, 2F5, 2G12, and 4E10, could neutralize the six Group O viruses tested between 62-97%. The 2F5 epitope in the O group viruses was : ELDEWA. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)
  - 2F5: This paper reviews MAbs that bind to HIV-1 Env. 2F5 binds to a region of gp41 proximal to cluster II (aa 662-676), neighboring the binding site of the broadly neutralizing MAb 4E10 and of neutralizing Fab Z13. 2F5 is broadly neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
  - 2F5: A set of oligomeric envelope proteins were made from six primary isolates for potential use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. 2F5 bound to clade A, B, D and F HIV-1 primary isolates. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004]
  - 2F5: 2F5 was used as a positive control in a study that showed that A32-rgp120 complexes open up the CCR5 co-receptor binding site, but did not induce neutralizing antibodies with greater breadth among B subtype isolates than did uncomplexed rgp120 in vaccinated guinea pigs. Liao *et al.* [2004]
  - 2F5: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. gp41 MAbs 246D, 98.6, 50-69, were decreased by trypsin, unaltered by thrombin, while NAb 2F5 binding was increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
  - 2F5: Mice susceptible to MV infection were intraperitoneally immunized with native HIV-1 89.6 env gp160 and gp140 and  $\delta$ V3 HIV-1 89.6 mutants expressed in live attenuated Schwarz measles vector (MV). The gp160 $\Delta$ V3 construct raised more cross-reactive NAb to primary isolates. The constructs had an additional 2F5 MAb epitope, ELDKWAS, but responses were not directed towards this epitope. A HIVIG/2F5/2G12 combination was used as a positive control and could neutralize all isolates. Lorin *et al.* [2004] (**vaccine antigen design**)
  - 2F5: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) and adjacent to the C-terminal end of the V3 loop (GM329 C3) did not alter neutralization susceptibility to 2F5, but the loss of glycans in C2 (GM292 C2), C4 (GM438 C4), or V5 (GM454 V5) increased 2F5 neutralization susceptibility. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure, vaccine antigen design**)
  - 2F5: This review summarizes properties of 2F5 and its binding to the prefusogenic membrane proximal region of gp41. The linear core epitope does not stimulate cross-reactive NAb when placed outside the context of gp41, suggesting its presentation in a highly specific molecular framework is critical. McGaughey *et al.* [2004] (**vaccine antigen design, review**)
  - 2F5: 2F5 was used for screening of phage-displayed peptide libraries. 2F5 requires the DKW core for synthetic and phage-displayed peptide recognition, but is multispecific for amino acid residues flanking C-terminally the DKW core epitope. Three clones from the AADKW-X12 library had high affinity for 2F5, but did not share obvious homology with gp41 or each other; Ala substitution showed each bound to 2F5 with a different mechanism. Menendez *et al.* [2004] (**antibody binding site definition and exposure, mimotopes**)
  - 2F5: A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4, R5, and X4 viruses were generated, and sCD4, 2G12 and b12 neutralization resistance patterns were modified by addition of the late stage V1V2, glycosylation changes, and charge in

concert, while neutralization by 2F5 was unaffected. Nabatov *et al.* [2004] (**antibody binding site definition and exposure, co-receptor**)

- 2F5: An antigen panel representing different regions of gp41 was generated, and sera from 23 individuals were screened. Anti-gp41 titers were very high, and sera bound to many regions of gp41, there were no immunologically silent regions. Many individuals had broad responses to diverse regions. High titer responses tended to focus on the N-heptad, C-heptad and 2F5-4E10 regions, but there was no correlation between neutralization capacity of sera and the particular peptides recognized. 2F5 responded to the four antigens that carried the minimal EDLKWA epitope. 2F5 did not bind to the minimal epitope embedded in an alpha helix, supporting that the 2F5 conformation of EDLKWA is embedded in a beta sheet. 2F5 bound better to a synthetic peptide containing the proximal regions than to the native gp41. Opalka *et al.* [2004] (**assay standardization/improvement**)
- 2F5: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 2F5: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. The IC50 for 2F5 was greater than 50 for CC1/85, and was 35 for CCcon19, so the passaged virus was weakly neutralized by 2F5. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization, viral fitness and reversion**)
- 2F5: The MAb 2F5 binds to the C-heptad and is neutralizing, but the MAb D50 binds to the C-heptad and is not neutralizing. 2F5 binds preferentially to native gp41 prior to receptor activation. D50 prefers the triggered form after receptor activation. Trapped fusion-intermediates suggest 2F5 remains present shortly after gp120 triggering by CD4, but may be lost by the time the six-helix bundle is formed. D50 binds equally to the fusion-intermediate and six-helix bundle. 2F5 neutralization seems to block a later step of the fusion process, but it does not inhibit binding of NC-1, a MAb specific for the six-helix bundle, so it does not prevent formation of the six-helix bundle. The results are most consistent with 2F5 inhibiting a post-fusion-intermediate step. de Rosny *et al.* [2004b] (**antibody binding site definition and exposure, antibody interactions**)
- 2F5: The mechanism of 2F5 neutralization was explored, and experiments suggest it is due to interference with a late step in viral entry. sCD4 binding to gp120 triggers conformational changes in gp41 allowing formation of the six helix bundle. The NAb 2F5 preferentially bound native gp41, prior to receptor triggering, while the antibody D50 that also binds to the heptad region, near 2F5, is not neutralizing, and preferentially bound the CD4-triggered gp41. The C and N peptides that can be used to block the formation of the six helix bundle and lock gp41 in the fusion intermediate state after sCD4 triggering enabled 2F5 to bind after sCD4, while D50 was able to bind to both the peptide-trapped and sCD4 induced six helix bundle equally well. The peptide-trapping studies suggest that 2F5 does not fix Env in the native conformation, but interferes with entry after the initial conformation changes occur. Nor does it block six-helix bundle formation, as 2F5 prebinding does not inhibit NC-1 binding, a MAb that binds specifically to the six-helix bundle. de Rosny *et al.* [2004a]
- 2F5: This review discusses research presented at the Ghent Workshop of prevention of breast milk transmission and immunoprophylaxis for HIV-1 in pediatrics (Seattle, Oct. 2002), and makes the case for developing passive or active immunoprophylaxis in neonates to prevent mother-to-infant transmission. Macaque studies have shown that passive transfer of NAb combinations (for example, IgG1b12, 2G12, 2F5, and 4E10; or 2G12 and 2F5) can confer partial or complete protection to infant macaques from subsequent oral SHIV challenge. Safrit *et al.* [2004] (**immunoprophylaxis, mother-to-infant transmission**)
- 2F5: A complex of the epitope peptide ELDKWAS bound to 2F5 was crystalized, and the peptide was found to interact with amino acids near the base of the very long (22 residue) CDR 3H region of the Ab. Ala substitution of the CDR H3 region confirmed the importance of these sites near the base of the H3 loop for interaction with the epitope in the context of intact gp41 as well as the peptide. A Phe at the apex of the loop was not located directly in the binding site, however binding of 2F5 to the epitope was very sensitive to non-conservative substitutions in this position (F100G, F100H, and F100R); these diminished both binding affinity and 2F5 neutralization, suggesting a role for the very long CDR 3H region. The authors suggest that particularly long CDR H3 regions may be a common feature of HIV-1 NAb, based on the 22 residues in H3 of 2F5, the 18 H3 residues in b12, and the 22 H3 residues in X5. They express concern that because small animals like mice are unable to elicit Ab responses with such long H3s, they may be poor model systems for HIV vaccine studies. Zwick *et al.* [2004] (**antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, structure**)
- 2F5: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. gp41 NAb 2F5 and 4E10 are able to potentially neutralize the SOS pseudovirion post-attachment, although 2F5 performed relatively poorly in the pre-attachment assay, a further support for previous studies that indicated it does not bind well to native Env, and may bind best after the virus is attached to cells. Binley



- et al.* [2003] (**vaccine antigen design**)
- 2F5: A sCD4-17b single chain chimera was made that can bind to the CD4 binding site, then bind and block co-receptor interaction. This chimeric protein is a very potent neutralizing agent, more potent than IgG1b12, 2G12 or 2F5 against Ba-L infection of CCR5-MAGI cells. It has potential for prophylaxis or therapy. Dey *et al.* [2003]
  - 2F5: Four newborn macaques were challenged with pathogenic SHIV 89.6 and given post exposure prophylaxis using a combination of NAbS 2F5, 2G12, 4E10 and IgG1b12. 2/4 treated animals did not show signs of infection, and 2/4 macaques maintained normal CD4+ T cell counts and had a lower delayed peak viremia compared to the controls. Ferrantelli *et al.* [2003] (**antibody interactions, immunoprophylaxis, mother-to-infant transmission**)
  - 2F5: This study investigates the effects of glycosylation inhibitors on the binding between HIV-1 gp120 and mannose-binding lectin (MBL). Mannosidase I inhibitor deoxymannojirimycin (dMM) inhibits formation of complex and hybrid N-linked saccharides and yields virus with more mannose residues. dMM added during viral production significantly enhanced the binding 2F5 and 2G12, but not IgG1b12 in a viral capture assay. Hart *et al.* [2003] (**antibody binding site definition and exposure**)
  - 2F5: MAbs IgG1b12, 2G12, 2F5 and 4E10 were tested for their ability to neutralize two primary HIV-1 clade A isolates (UG/92/031 and UG/92/037) and two primary HIV-1 clade D isolates (UG/92/001 and UG/92/005). 4E10 demonstrated the most potent cross-neutralization activity. Quadruple administration of MAbs IgG1b12, 2G12, 2F5, and 4E10 induced strong synergistic neutralization of 4 clade A isolates (UG/92/031, UG/92/037, RW/92/020 and RW/92/025) as well as 5 clade D isolates (UG/92/001,UG/9/005, /93/086/RUG/94/108, UG/94/114). The authors note this combination of 4 MAbs neutralizes primary HIV A, B, C, and D isolates. Kitabwalla *et al.* [2003] (**antibody interactions, immunoprophylaxis, variant cross-recognition or cross-neutralization, mother-to-infant transmission, subtype comparisons**)
  - 2F5: This review discusses the importance and function of protective antibody responses in animal model studies in the context of effective vaccine development. SHIV models have shown protection using high levels of MAbs can prevent infection, and partial protection that can influence disease course can be obtained from modest levels of NAbS. SHIV challenges studies conducted with infusions of combinations of MAbs b12, 2G12, and 2F5 are reviewed. Mascola [2003] (**immunoprophylaxis, review**)
  - 2F5: Infusions of 2F5 and 2G12 intravenously administered 24h prior to vaginal SHIV-89.P challenge are able to protect macaques from infections. Animals that receive a IL-2 adjuvanted DNA immunization SIV Gag and HIV Env have T-cell responses and lower viral loads, but were not protected. Sub-optimal levels of 2F5 and 2G12 were not able to confer sterile protection in combination with the T-cell responses stimulated by DNA immunizations. Mascola *et al.* [2003] (**adjuvant comparison, vaccine-specific epitope characteristics**)
  - 2F5: Cyclic peptides ELLELDKWASLW that adopt constrained beta-turn conformation of the 2F5 epitope beta-turn in the complexed crystal structure were synthesized and optimized 2F5 binding affinity. This peptide elicits high titer peptide-specific immune responses in guinea pigs that do not neutralize; the authors propose this may be the result of a short CDR3 loop in guinea pigs. McGaughey *et al.* [2003] (**antibody binding site definition and exposure, vaccine antigen design, binding affinity, structure**)
  - 2F5: AC10 is a subject who was given treatment early after infection, and had a viral rebound after cessation of therapy, which then declined to a low level. The polyclonal sera from AC10 could potentially neutralize the rebound virus, and NAb escape followed with a neutralizing response against the escape variant and subsequent escape from that response. Viral loads remained low in this subject despite escape. The rebound isolate that was potentially neutralized by autologous sera was not particularly neutralization sensitive, as it resisted neutralization by sCD4 and MAbs IgG1b12, 2G12 and 2F5, and was only moderately sensitive to sera from other HIV+ individuals that had high titers of NAbS to TCLA strains. Montefiori *et al.* [2003] (**acute/early infection, escape**)
  - 2F5: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. 2F5 recognized most variants from 3/4 individuals by gp41 WB; the 4th individual had the ELDKWA variant Aldkwa in all three isolates. The other single Env that was not recognized carried eldRwa. Ohagen *et al.* [2003] (**brain/CSF, escape**)
  - 2F5: Most plasma samples of patients from early infection had NAb responses to early autologous viruses, and NAbS against heterologous strains tended to be delayed. Serial plasma samples were tested against serial isolates, and neutralization escape was shown to be rapid and continuous throughout infection. Autologous neutralization-susceptible and resistant viruses from four patients were tested for susceptibility to neutralizing Ab responses using MAbs 2G12, IgG1b12 and 2F5. No correlation was established, all viruses tested were susceptible to at least one of the neutralizing MAbs. Two patients that did not have an autologous NAb response also did not evolve changes in susceptibility to these MAbs, while one patient with a pattern of autologous neutralization and escape acquired a 2G12 sensitive virus at month 6, and lost IgG1b12 sensitivity at month 21. Richman *et al.* [2003] (**autologous responses, acute/early infection, escape**)
  - 2F5: Review of current neutralizing antibody-based HIV vaccine candidates and strategies of vaccine design. Strategies for targeting of the epitopes for NAbS 2F5, 2G12, 4E10, b12, and Z13 are described. Wang [2003] (**vaccine antigen design, review**)
  - 2F5: The broadly neutralizing antibodies 2F5 and 2G12 were class-switched from IgG to IgA and IgM isotypes. Neutralizing potency was increased with valence for 2G12 so the IgM form was most potent, but for 2F5 the IgG form was most potent. Eight primary isolates were tested including two subtype A isolates. The polymeric IgM and IgA Abs, but not the corresponding IgGs, could interfere with HIV-1 entry across a mucosal epithelial layer, although they were limited in a stan-

standard neutralization assay. All isotypes could interact with activated human sera, presumably through complement, to inhibit HIV replication. Wolbank *et al.* [2003] (**complement, isotype switch, variant cross-recognition or cross-neutralization, mucosal immunity, subtype comparisons**)

- 2F5: A combination of MAbs 2F5 and 2G12 given in multiple infusions was found to be safe and well tolerated even in high doses in a phase I study of seven HIV-1 infected healthy volunteers—the median elimination half-life was 7.94 days for 2F5, and 16.48 for 2G12—no anti-2F5 or anti-2G12 IgM or IgG responses were detected—although there was some transient increases, overall plasma viral RNA levels decreased in 6/7 volunteers, by a median of 0.62 log<sub>10</sub>. Armbruster *et al.* [2002] (**immunotherapy**)
- 2F5: IgG1b12 neutralized many South African (5/8) and Malawian (4/8) clade C primary HIV-1 isolates, being more effective than 2F5 which neutralized only two Malawian and no South African isolates. 2G12 did not neutralize any of the 16 isolates. Bures *et al.* [2002] (**subtype comparisons**)
- 2F5: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate, with the exception of F240 which bound both equally well, which captured more virus than any other human MAb tested, and didn't neutralize either isolate. F240 enhanced the binding of CD4BS MAbs IgG1b12 and F105 and the gp41 MAb 2F5 for both R5X4 and R5 isolates. F240 also enhanced neutralization of the R5X4 isolate by 2F5, but had no effect on R5 virus. Anti-V3 MAb B4a1 did not impact 2F5 neutralization. Cavacini *et al.* [2002] (**antibody binding site definition and exposure, antibody interactions, co-receptor**)
- 2F5: A modified gp140 (gp140deltaCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation, retained antigenic conformational determinants as defined by binding to CD4 and to MAbs 2F5, 2G12, F105, and b12, and enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002] (**vaccine antigen design**)
- 2F5: Six sera from HIV-exposed uninfected individuals (EU) had IgA neutralizing activity dominated by recognition of a distinctive epitope within gp41, QARILAV – sera of QAFILAV-immunized BALB/c mice was neutralizing with the dose-dependent behavior similar to 2F5. Clerici *et al.* [2002a] (**HIV exposed persistently seronegative (HEPS)**)
- 2F5: Review of NAbs that notes that 2F5 alone or in combination with other MAbs can protect some macaques against SHIV infection, that it is safe and well tolerated in humans, and that illustrates gp41's conformational change and exposure of the 2F5 epitope in the transient pre-hairpin form. Ferrantelli & Ruprecht [2002] (**immunoprophylaxis, review**)
- 2F5: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I and Cluster II MAbs required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor, binding to a fusion intermediate. 2F5 behaved very differently than these non-neutralizing antibodies: it bound to Env in the absence of target cells, and it was distributed evenly all over the cell surface, not localized in fusion domains. It did not interact with cells that exhibited cytoplasmic mixing. 2F5 was unusual in that it exhibited temperature dependence, and did not interact below 19 degrees C, in contrast to 2G12, M77 98-6 and IgG1b12 which bound strongly at temperatures ranging between 4-37 degrees. The authors suggest the temperature dependence of 2F5 may be due to increased flexibility of the Envelope spike at warmer temperatures facilitating epitope exposure. Finnegan *et al.* [2002] (**antibody binding site definition and exposure, kinetics**)
- 2F5: Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 sensitivity is increased in the mutated viruses, presumably because 2F5's neutralization activity is focused on the transition to the fusion active state. No other MAb against gp41 tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- 2F5: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b. Golding *et al.* [2002b]
- 2F5: UK1-br and MACS2-br are R5 isolates derived from brain tissue samples from AIDS patients with dementia and HIV-1 encephalitis; both are neurotropic, but only UK1-br induced neuronal apoptosis and high levels of syncytium formation in macrophages. UK1-br Env had a greater affinity for CCR5 than MACS-br, and required low levels of CCR5 and CD4 for cell-to-cell fusion and single round infection. PBMC infected with UK1-br and MACS2-br virus isolates were resistant to neutralization by MAb 2G12. UK1-br was more sensitive than MACS2-br to IgG1b12, 2F5 and CD4-IgG2 neutralization. This pattern of Ab reactivity was similar to the CD4-independent variant ADA197N/K, and thought to result from conformational changes which better expose the CCR5 binding regions, although the loss of the particular N-linked glycosylation site in the V1V2 stem region of ADA was experimentally shown to not be responsible for the CD4-independent phenotype of UK1-br. Gorry *et al.* [2002] (**brain/CSF, co-receptor**)
- 2F5: HIV-1 gp160ΔCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines—2F5 bound to gp160ΔCT with a reconstituted membrane ten-fold better than the same protein on beads (except for the YU2 form that doesn't bind 2F5)—anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160ΔCT PLs indis-

- tinguishably from gp160 $\Delta$ CT expressed on the cell surface. Grundner *et al.* [2002] (**vaccine antigen design**)
- 2F5: ELDKWAS was embedded into a beta-turn-like conformational site on a framework of an antibody specific for human leukocyte antigen HLA-DR – this construct was recognized by 2F5, and is suggested as an adjuvant-independent vaccine candidate. Ho *et al.* [2002] (**vaccine antigen design**)
  - 2F5: A mouse MAb was raised against a variant of ELDKWA core epitope of the NAb 2F5, eldEwa, derived from the 2F5 neutralization resistant variant MVP5180. 2F5 does not bind to the variants eldEwa, elNkwa (B.TH.TH936705) or elEkwa, while 14D9 binds only to eldEwa and not ELDKWA. The eldEwa variant is common in the HIV-1 O group. Huang *et al.* [2002] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 2F5: DP178 is a peptide derived from the C-term heptad repeat of gp41 that is a potent inhibitor of viral-mediated fusion—it contains the 2F5 epitope but fails to stimulate 2F5-like NAb upon immunization—the peptide was extended to force an increase in helicity, and the modified peptide had a increase in affinity for 2F5, but upon guinea pig immunization although high peptide-specific Ab titers were achieved the sera were incapable of viral neutralization—the authors propose that 2F5 may bind with low affinity to a maturation intermediate, which may account for its breadth and why it is hard to recreate the epitope, but also suggests that the high concentrations required for neutralization are not relevant *in vivo*. Joyce *et al.* [2002] (**antibody binding site definition and exposure**)
  - 2F5: A 2F5 anti-idiotypic murine MAb Ab2/3H6 was developed that blocks 2F5 binding to a synthetic epitope peptide and to gp160 in an ELISA competition assay – Ab2/3H6 diminished the neutralizing potency of 2F5 – Ab2/3H6 Fab fragments were capable of inducing neutralizing Abs and 2F5-epitope specific responses in immunized B6D2F1 mice. Kunert *et al.* [2002] (**vaccine antigen design**)
  - 2F5: A polyepitope vaccine was designed based on three repeats of the 2F5 core epitope ELDKWA combined with the V3 region peptide GPGRAFY. Abs raised in mice could recognize the peptides, sgp41, and CHO-WT cells that expressed HIV-1 Env on their surface. Li *et al.* [2002] (**vaccine antigen design**)
  - 2F5: Review of NAb that discusses mechanisms of neutralization, passive transfer of NAb and protection in animal studies, and vaccine strategies. Liu *et al.* [2002] (**immunoprophylaxis, vaccine antigen design, review**)
  - 2F5: Rhesus macaques were better protected from vaginal challenge with SHIV89.6D (MAb 2G12, 2/4; MAbs 2F5/2G12, 2/5; and HIVIG/2F5/2G12, 4/5 infected) than from intravenous challenge (MAb 2G12, 0/3; MAbs 2F5/2G12, 1/3; and HIVIG/2F5/2G12, 3/6 infected)—the animals that were infected by vaginal challenge after Ab infusion had low or undetectable viral RNA levels and modest CD4 T-cell decline. Mascola [2002] (**immunoprophylaxis**)
  - 2F5: ELDKWAS co-crystallized bound to the Fab' 2F5 fragment showed the epitope peptide in a type I beta-turn conformation. Pai *et al.* [2002] (**structure**)
  - 2F5: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAb 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140 – SOS gp140-2F5-IgG1b12 formed multiple ring structures composed of two SOS gp140 proteins bridged by two Ab molecules, while 2F5 and 2G12 formed extended chains rather than closed rings. Schulke *et al.* [2002] (**vaccine antigen design**)
  - 2F5: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – 2F5 recognized o-gp140. Srivastava *et al.* [2002] (**vaccine antigen design**)
  - 2F5: The antiviral response to intravenously administered MAbs 2F5 and 2G12 was evaluated in 7 HAART-naive asymptomatic HIV-1 infected patients during a treatment period of 28 days. MAb therapy reduced plasma HIV RNA in 3/7 patients during the treatment period, and transiently reduced viral load in two more. CD4 counts were up in 3/7 through day 28, and transiently increased in three more. Vigorous complement activation was observed after 48/56 Ab infusions. Before treatment, 2F5 neutralized isolates from five patients and no escape was observed during treatment. Stiegler *et al.* [2002] (**complement, variant cross-recognition or cross-neutralization, escape, immunotherapy**)
  - 2F5: Expanding the minimal epitope ELDKWA to an end-capped, linear nonapeptide, Ac-LELDKWASL-amide attained maximal affinity within a set of native gp41-sequence peptides – scanning single residue substitutions confirmed that essential recognition requirements were the central DKW core sequence and the importance of the terminal Leu residues for high-affinity binding – high specificity binding pockets at central Lys and Trp side-chains and an absolute requirement for the carboxylate group of the Asp side chain were found – the nine residue fragment flanked by pairs of Ser and constrained by a disulfide bridge had high affinity for 2F5. Tian *et al.* [2002] (**antibody binding site definition and exposure**)
  - 2F5: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b]
  - 2F5: Passive immunization of neonate macaques with a combination of F105+2G12+2F5 conferred complete protection against oral challenge with SHIV-vpu+ or – the combination b12+2G12+2F5 conferred partial protection against SHIV89.6 – such combinations may be useful for prophylaxis at birth and against milk born transmission – the synergistic

- combination of IgG1b12, 2G12, 2F5, and 4E10 neutralized a collection of HIV clade C primary isolates. Xu *et al.* [2002] (**antibody interactions, immunoprophylaxis, subtype comparisons**)
- 2F5: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
  - 2F5: ELNKWA is an escape variant not recognized by the broadly neutralizing MAb 2F5, which recognizes the core epitope ELDKWA – Abs were raised against the peptide escape variant CGELNKWAGELNKWA linked to KLH carrier – these polyclonal antibodies, like the monoclonal antibody TH-Ab1 also raised to ELNKWA, could recognize ELDKWA and escape mutant peptide epitopes ELEKWA and ELDEWA. Dong *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
  - 2F5: A combination of MAbs IgG1b12, 2F5, and 2G12 was given postnatally to four neonates macaques that were then challenged with highly pathogenic SHIV89.6P – one of the four infants remained uninfected after oral challenge, two infants had no or a delayed CD4(+) T-cell decline. Hofmann-Lehmann *et al.* [2001] (**immunoprophylaxis**)
  - 2F5: Mutations in two glycosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYRLINCNTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, including to antibody 2F5. Kolchinsky *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
  - 2F5: Review of studies in macaques that have shown immune control of pathogenic SHIV viremia, improved clinical outcome, and protection, and the implications of the observations for HIV vaccines. Mascola & Nabel [2001] (**review**)
  - 2F5: Moore and colleagues review the data concerning the lack of a clear relationship between genetic subtype and serotype – 2F5 is considered in some detail, as it represents a rare vulnerability from the neutralizing antibody perspective, although while it is apparently linear, attempts to present the peptide to the immune system have failed to elicit neutralizing Abs. Moore *et al.* [2001] (**review, subtype comparisons**)
  - 2F5: Matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) in combination with proteolytic protection was used to identify the functional epitope for MAb 2F5, NEQELLELDKQASLWN, in the disulfide bond associated gp120/gp41 protein SOS-gp140 (JRFL) – this minimal epitope is much larger than the ELDKWA core epitope previously defined by peptide ELISA, and this could help explain why ELDKWA-peptides are poor immunogens in terms of eliciting a 2F5-like antibody response. Parker *et al.* [2001] (**antibody binding site definition and exposure**)
  - 2F5: A peptide called 5-Helix was designed that binds to the C-peptide region of gp41 – 5-Helix is a potent inhibitor of HIV-1 entry that binds immediately COOH-terminal to the C-peptide region targeted by 5-Helix – the conformation of the bound 2F5 epitope is a hairpin turn. Root *et al.* [2001]
  - 2F5: SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkey's yielded highly pathogenic SHIV KU-1 – HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160 – substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1 – 17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001]
  - 2F5: A luciferase-reporter gene-expressing T-cell line was developed to facilitate neutralization and drug-sensitivity assays – luciferase and p24 antigen neutralization titer end points were found comparable using NAb from sera from HIV+ donors, and MAbs 2F5, 2G12 and IgG1b12. Spenlehauer *et al.* [2001] (**assay development**)
  - 2F5: 4E10 binds proximal to 2F5 and neutralizes primary isolates of clades A, B, C, D, and E – viruses that were resistant to 2F5 were neutralized by 4E10 and vice versa. Stiegler *et al.* [2001] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 2F5: A phage peptide library was screened with MAb 2F5, and from the peptides that bound the amino acids DKW were found to be most critical for binding – the mimetic peptide RDWSFDRWLSLSEFWL elicited a cross-reactive Ab response to gp41 when used to immunize rabbits. Tumanova *et al.* [2001]
  - 2F5: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions, variant cross-recognition or cross-neutralization**)
  - 2F5: Twenty HIV clade C isolates from five different countries were susceptible to neutralization by anti-clade B MAbs in a synergistic quadruple combination of mAbs IgG1b12, 2G12, 2F5, and 4E10. Xu *et al.* [2001] (**antibody interactions**)
  - 2F5: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
  - 2F5: Neutralizing synergy between MAbs 1b12, 2G12 and 2F5 was studied using surface plasmon resonance to determine the binding kinetics for these three mAbs with respect to monomeric and oligomeric env protein gp160 IIIB – the

- 2G12 epitope is highly accessible on both monomeric and oligomeric Envs, 1b12 is highly accessible on monomers but not oligomers, and 2F5 on neither form – binding of 2G12 exposes the 2F5 epitope on gp160 oligomers. Zeder-Lutz *et al.* [2001] (**antibody interactions**)
- 2F5: This paper primarily concerns 4E10 and Z13, MAbs that both bind proximally to the 2F5 binding site to a conserved epitope, and that neutralize some primary isolates from clades B, C, and E – the minimal 2F5 epitope is determined to be EQELLELDKQASLW, based on screening a gp160 fragment expression library, longer than previous studies – broadly neutralizing MAbs 2F5, IgG1b12, and 4E10 and Z13 fail to neutralize different subsets of viruses. Zwick *et al.* [2001b] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 2F5: Neutralization synergy between anti-HIV NAb b12, 2G12, 2F5, and 4E10 was studied – a classic fixed-ratio method was used, as well as a method where one Ab was fixed at a low neutralization titer and the other was varied – using primary isolates, a two-four fold enhancement of neutralization was observed with MAb pairs, and a ten-fold enhancement with a quadruple Ab combination – no synergy was observed with any MAb pair in the neutralization of TCLA strain HXB2. Zwick *et al.* [2001c] (**antibody interactions**)
  - 2F5: Paper uses IgG1 form of 2F5 – a triple combination of 2F5, F105 and 2G12 effectively neutralized perinatal infection of macaque infants when challenged with SHIV-vpu+ – the plasma half-life was 4.2 +/- 0.8 days. Baba *et al.* [2000] (**immunoprophylaxis**)
  - 2F5: MAbs 98-6 and 2F5 both bind to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, and to C43 alone but not to N51 alone – 98-6 and 2F5 have comparable affinities for C43, but 98-6 has a higher affinity for the complex and 2F5 may bind to an epitope of C43 that is directly involved with complex formation – and IgG1 rec form of the Ab was used in this study. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
  - 2F5: 2F5 is a candidate for immunotherapy, but generally IgG1 has a longer half life in humans than IgG3, so the isotype was switched – rec CHO-derived MAb 2F5 IgG1kappa and hybridoma-derived MAb 2F5 IgG3kappa displayed identical specificity, *in vitro* function, and epitope (ELDKWA) – it remains to be determined if isotype switching will prolongs beta-clearance. Kunert *et al.* [2000] (**immunotherapy**)
  - 2F5: Low levels of anti-ELDKWA antibodies are observed in HIV-1 + individuals, so a C-domain P2 peptide linked to a carrier was used to immunize mice and rabbits, and stimulated a high-level anti-ELDKWA response. Liao *et al.* [2000] (**vaccine antigen design**)
  - 2F5: ELDKWA peptide vaccine study. Lu *et al.* [2000c] (**vaccine antigen design**)
  - 2F5: ELDKWA peptide vaccine study. Lu *et al.* [2000b] (**vaccine antigen design**)
  - 2F5: Because HIV-1 is most often transmitted across mucosal surfaces, the ability of passive transfer of infused HIVIG/2F5/2G12 to protect against mucosal exposure of macaques to pathogenic SHIV 89.6PD was studied – HIVIG/2F5/2G12 protected 4/5 animals against vaginal challenge, 2F5/2G12 combined protected 2/5 animals, and 2G12 alone protected 2/4 animals – in contrast, Mascola and co-workers had previously shown single MAbs could not protect against intervenous challenge – Ab treated animals that got infected through vaginal inoculation had low viral loads and only modest declines in CD4 counts – the infused Abs were detected in the nasal, vaginal, and oral mucosa. Mascola *et al.* [2000] (**immunoprophylaxis, mucosal immunity**)
  - 2F5: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 cluster II anti-gp41 MAbs – of these 2F5, 167-D, 126-6, and 1281 bound across clades, but usually weakly, while 98-6 and 1342 had poor cross reactivity – Clade D isolates bound most consistently to cluster II MAbs. Nyambi *et al.* [2000] (**subtype comparisons**)
  - 2F5: A mini-review of observations of passive administration of IgG NAb conferring protection against intervenous or vaginal SHIV challenge, that considers why IgG MAbs might protect against mucosal challenge. Robert-Guroff [2000] (**review**)
  - 2F5: 2F5 or sCD4-IgG chimeric immunoadhesin were transferred into 3T3 cells, incorporated into a collagen structure called the neo-organ, and transplanted into SCIDhu mice that were then challenged with MN or LAI – the continuous production of the therapeutic molecules in this context resulted in dramatic reduction of viral load. Sanhadji *et al.* [2000] (**immunotherapy**)
  - 2F5: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – gp41 MAbs T4, D12, T3, and D50 bound less efficiently to gp140-GNC4 than did pooled sera, but T4 and D12 recognized the gp140-GNC4 trimer equivalently to gp140(-), and T3 and D50 recognized the trimer at greater levels than gp140(-) – 2F5 did not bind efficiently to these constructs, presumably because of the YU2 strain has a substitution in the 2F5 epitope (ALDKWA instead of ELDKWA). Yang *et al.* [2000] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)
  - 2F5: rgp120 derived from a R5X4 subtype B virus was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs. Beddows *et al.* [1999]
  - 2F5: Combinations of HIVIG, 2F5, 2G12 were administered in passive-transfer experiments 24 hours prior to challenge with pathogenic SHIV 89.6PD – 3/6 animals given HIVIG/2F5/2G12 were completely protected, the others had reduced viremia and normal CD4 counts – 1/3 monkeys given 2F5/2G12 showed transient infection, the other two had reduced viral load – all monkeys that received HIVIG, 2F5, or 2G12 alone became infected and developed high-level plasma viremia, although animals that got HIVIG or 2G12 had a less profound CD4 T cell decline. Mascola *et al.* [1999] (**immunoprophylaxis**)
  - 2F5: A meeting summary presented results regarding neutralization – MAbs 2G12 and 2F5 tested for their ability to neutralize primary isolate infection of genetically engineered cell lines (cMAGI and others, presented by T. Matthews, A. Trkola, J. Bradac) – an advantage of such cells lines over

PBMCs is that markers (X-Gal) can be added for staining to simplify the assay – the consensus of the meeting was that these engineered cell lines did not improve the sensitivity of detection of primary isolate neutralization – D. Burton and J. Mascola presented results concerning passive immunization and protection of hu-PBL-SCID mice and macaques, respectively, and both found combinations of MABs that were able to achieve 99% neutralization *in vitro* corresponded to efficacy *in vivo*. Montefiori & Evans [1999] (**review**)

- 2F5: In a study of 116 HIV-1 + individuals, Ab reactivity to a peptide encompassing the ELDKWA peptide decreased in CDC stage C patients compared with stage A patients, and longitudinal studies showed a decline in 6/8 patients, while overall Ab reactivity to rec soluble gp160 stayed constant. Muhlbacher *et al.* [1999]
- 2F5: Review of the neutralizing Ab response to HIV-1. Parren *et al.* [1999] (**review**)
- 2F5: Hu-PBL-SCID mice were infected with HIV-1s JRCSF and SF162 to study the effect of NABs on an established infection – no significant differences in the initial rate of decrease in viral load or the plateau levels of viral RNA between the b12 treated and control mice were seen – in most of the Ab treated mice b12 escape mutants were observed with varying patterns of mutations – a combination of b12, 2G12 and 2F5 protected 1/3 mice, and an isolate from one of the other two was resistant to neutralization by all three MABs. Poignard *et al.* [1999] (**immunotherapy**)
- 2F5: Post-exposure prophylaxis was effective when MAb 694/98-D was delivered 15 min post-exposure to HIV-1 LAI in hu-PBL-SCID mice, but declined to 50% if delivered 60 min post-exposure, and similar time constraints have been observed for HIVIG, 2F5 and 2G12, in contrast to MAb BAT123 that could protect delivered 4 hours post infection. Andrus *et al.* [1998] (**immunoprophylaxis**)
- 2F5: Ab from gp120 vaccinated individuals prior to infection, who subsequently became HIV infected, could not achieve 90% neutralization of the primary virus by which the individuals were ultimately infected – these viruses were not particularly refractive to neutralization, as determined by their susceptibility to neutralization by MABs 2G12, IgG1b12, 2F5 and 447-52D. Connor *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 2F5: The ELDKWA epitope was inserted into the antigenic site B of influenza hemagglutinin and expressed on baculovirus infected insect cells, flanked by 3 additional random amino acids, xELDKWaxx – FACS was used to isolate the clone that displayed the epitope with the most markedly increased binding capacity for 2F5, to identify particularly specific immunogenic constructs – PELDKWAPP was a high affinity form selected by FACS. Ernst *et al.* [1998] (**vaccine antigen design**)
- 2F5: Points out that 2G12 and 2F5, potent neutralizing antibodies, were identified by screening for cell surface (oligomeric Envelope) reactivity. Fouts *et al.* [1998]
- 2F5: Infection of dendritic cells cultured from CD14+ blood cells or from cadaveric human skin was blocked by neutralizing MABs IgG1b12, or 2F5 and 2G12 delivered together, but not by control non-neutralizing anti-gp120 MAB 4.8D, indicating that NABs could interrupt early mucosal transmission events. Frankel *et al.* [1998] (**mucosal immunity**)
- 2F5: The natural immune response to the epitope of 2F5, ELDKWA, was studied in perinatally infected children and levels of reactivity to this epitope were correlated with absolute CD4 numbers over time and health status – 3/10 children who had no antibody reactivity to ELDKWA had substitutions in the epitope (ALDKWA, ELDQWA, and KLDKWA) – 2F5 competed with the ELDKWA-reactive sera depending on the serum titer. Geffin *et al.* [1998]
- 2F5: Used as a control in the study of anti-gp41 MAB NC-1 – 2F5 does not react with HIV-2 gp41 or gp160. Jiang *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 2F5: The complete V, J and D(H) domain was sequenced – unlike non-neutralizing anti-gp41 MAB 3D6, five neutralizing MABs (2F5, 2G12, 1B1, 1F7, and 3D5) showed extensive somatic mutations giving evidence of persistent antigenic pressure over long periods – in contrast to Geffin98, where multiple pediatric sera were found to compete with 2F5, cross-competition was noted to be very rare in sera from HIV+ adults – Kunert *et al.* propose that because there is a binding site of human complement factor H which overlaps the 2F5 binding site, it may generally be masked from the immune system – 2F5 also has a remarkably long CDR3 loop of 22 amino acids, and this region could not be readily assigned to any described D(H) fragment, leading to the suggestion of recombination of two fragments from novel regions. Kunert *et al.* [1998] (**antibody sequence variable domain**)
- 2F5: Neutralization synergy was observed when the MABs 694/98-D (V3), 2F5 (gp41), and 2G12 (gp120 discontinuous) were used in combination, and even greater neutralizing potential was seen with the addition of a fourth MAB, F105 (CD4 BS). Li *et al.* [1998] (**antibody interactions**)
- 2F5: This MAB and the results of Ugolini *et al.* [1997] are discussed – the authors propose that an Ab bound to gp41 would typically project less from the surface of the virion and so be unable to interfere with attachment Parren *et al.* [1998a]. Parren *et al.* [1998a]; Ugolini *et al.* [1997] (**review**)
- 2F5: MABs 2G12, 2F5 and b12 are broadly neutralizing, as are some human polyclonal sera, but this paper describes a set of primary isolates that are resistant to all three MABs and 2 broadly neutralizing sera – results indicate that resistance levels of pediatric isolates might be higher than adult isolates – resistance in general did not seem to be conferred by a loss of binding affinity for gp120 or gp41, rather by a more global perturbation of oligomeric Envelope. Parren *et al.* [1998b] (**variant cross-recognition or cross-neutralization**)
- 2F5: Induces complement-mediated lysis in MN but not primary isolates – primary isolates are refractive to CML. Takefman *et al.* [1998] (**complement**)
- 2F5: A wide range of neutralizing titers was observed that was independent of co-receptor usage – 2F5 was the most potent of the MABs tested. Trkola *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 2F5: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on

- tests with 6 MAbs and 5 isolates. Yang *et al.* [1998] (**assay development**)
- 2F5: This review summarizes results about 2F5: it binds extracellularly, near the transmembrane domain, it is the only gp41 MAb that is neutralizing, it reacts with many non-B clade viruses and has a paradoxically weak binding to virus, given the neutralizing titers. Burton & Montefiori [1997] (**review**)
  - 2F5: In a multilab evaluation of monoclonal antibodies, only IgG1b12, 2G12, and 2F5 could neutralize at least half of the 9 primary test isolates at a concentration of < 25 mug per ml for 90% viral inhibition – the isolates with no 2F5 neutralizing susceptibility had the sequences ALGQWA or ELDTWA instead of EDLKWA – 7/9 primary isolates were neutralized, and ALDKWQ and ALDKWA were susceptible to neutralization. D'Souza *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
  - 2F5: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB Env – strong neutralizer of SHIV-vpu+ – all Ab combinations tested showed synergistic neutralization – 2F5 has synergistic response with MAbs 694/98-D (anti-V3), 2G12, b12, and F105. Li *et al.* [1997] (**antibody interactions**)
  - 2F5: Using concentrations of Abs achievable *in vivo*, the triple combination of 2F5, 2G12 and HIVIG was found to be synergistic to have the greatest breadth and magnitude of response against 15 clade B primary isolates. Mascola *et al.* [1997] (**antibody interactions, variant cross-recognition or cross-neutralization**)
  - 2F5: A JRCSF variant that was selected for IgG1b12 resistance remained sensitive to MAbs 2G12 and 2F5, for combination therapy. Mo *et al.* [1997] (**antibody interactions**)
  - 2F5: Review: MAbs 2F5, 2G12 and IgG1b12 have potential for use in combination with CD4-IgG2 as an immunotherapeutic or immunoprophylactic – homologous MAbs to these are rare in humans and vaccine strategies should consider including constructs that may enhance exposure of these MAbs' epitopes. Moore & Trkola [1997] (**review**)
  - 2F5: Called IAM 2F5 – antibody mediated enhancement or inhibition seemed to be determined by isolate rather than antibody specificity – in this study, only 2F5 inhibited the entry of all the viruses studied, irrespective of their phenotype, and directly proportional to its affinity to monomeric HIV-1 gp160. Schutten *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
  - 2F5: Of three neutralizing MAbs (257-D, IgG1b12, and 2F5), 2F5 was the only one to inhibit the entry of all viruses studied, both SI and NSI, with a potency proportional to its affinity for monomeric gp126. Schutten *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
  - 2F5: Binding of anti-gp120 MAbs IgG1b12 or 654-30D does not mediate significant exposure of the gp41 epitopes for MAbs 2F5 and 50-69. Stamatatos *et al.* [1997] (**antibody interactions**)
  - 2F5: Used to standardize polyclonal response to CD4 BS. Turbica *et al.* [1997]
  - 2F5: The only MAb out of a large panel to show no correlation between viral binding inhibition and neutralization. Ugolini *et al.* [1997]
  - 2F5: IgG1b12 was more potent with greater breadth than MAb 2F5 in an infection reduction assay including 35 primary isolates. Kessler II *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
  - 2F5: Only 4/20 Argentinian and 3/43 Swedish HIV+ sera reacted with LLELDKWASL – sera reacting with peptides that contained EDLKWA tended to have high neutralization titers – the region carboxyl terminal to EDLKWA was found to be more important for polyclonal sera AB binding, 670-675 WN-WFDI – 2F5 bound most strongly to the peptide QELLELDKWA. Calarota *et al.* [1996] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 2F5: 2F5 was infused into two chimpanzees which were then given an intravenous challenge with a primary HIV-1 isolate – both became infected, but with delayed detection and prolonged decrease in viral load relative to controls, indicating that preexisting, neutralizing antibodies (passively administered or actively elicited) affect the course of acute-phase virus replication and can be influential after the Ab can no longer be detected in the peripheral circulation. Conley *et al.* [1996] (**immunoprophylaxis**)
  - 2F5: Neutralizes HXB2, primary isolates, and chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
  - 2F5: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996] (**immunotoxin**)
  - 2F5: Review: one of three MAbs (IgG1b12, 2G12, and 2F5) generally accepted as having significant potency against primary isolates. Poignard *et al.* [1996b] (**review**)
  - 2F5: Primary isolates from clade A, B, and E are neutralized by 2F5 – neutralization requires the LDKW motif – neutralization resistant isolates or 2F5 selected variants all had substitutions in the D or K. Purtscher *et al.* [1996] (**subtype comparisons**)
  - 2F5: Review: only four epitopes have been described which can stimulate a useful neutralizing response to a broad spectrum of primary isolates, represented by the binding sites of MAbs: 447-52-D, 2G12, Fab b12, and 2F5. Sattentau [1996] (**review**)
  - 2F5: ELDKWAS is in a gp41 binding region for the negative regulator of complement factor H (CFH) – Abs to HIV generally do not cause efficient complement-mediated lysis, but binding of 2F5 can interfere with CHF binding, facilitating HIV destruction by complement. Stoiber *et al.* [1996] (**complement**)
  - 2F5: Found to neutralize MN, JRCSF, and two B subtype primary isolates, but not a D subtype primary isolate, by most labs in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 2F5: Broad cross-clade neutralization of primary isolates – additive neutralization in combination with anti-CD4BS MAb IgG1b12 (Called BM12). Kessler *et al.* [1995] (**subtype comparisons**)

- 2F5: Review: binds to the only generally accepted strong neutralizing epitope outside of gp120, one of only 3 MAbs with strong broad activity against primary viruses, the others are 2G12 and IgG1b12 – unique member of epitope cluster Moore & Ho [1995] and John Moore, per comm 1996. Moore & Ho [1995] (**review**)
- 2F5: MAb binding decreases the accessibility or alters the conformation of the gp41 fusion domain and of gp120 domains, including the binding site for the CD4 cell receptor. Neurath *et al.* [1995] (**antibody binding site definition and exposure**)
- 2F5: Called IAM 41-2F5 – exposed in the presence of gp120 on the cell surface, while most of gp41 is masked – binds proximal to transmembrane region. Sattentau *et al.* [1995] (**antibody binding site definition and exposure**)
- 2F5: Cross-clade primary virus neutralizing activity – LDKW defined as the core epitope. Trkola *et al.* [1995] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- 2F5: MAb generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)
- 2F5: Called IAM-41-2F5 – neutralized lab and primary isolates – t 1/2 dissociation 122 min for the peptide, and 156 min for gp41 – core D(K/R)W – Ab resistant isolate had the sequence KLDNWA. Conley *et al.* [1994b] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 2F5: Included in a multi-lab study for antibody characterization binding and neutralization assay comparison. D'Souza *et al.* [1994] (**assay development**)
- 2F5: Failed to show synergy with anti-CD4 binding site IIIB neutralizing antibodies. Laal *et al.* [1994] (**antibody interactions**)
- 2F5: 2F5 epitope ELDKWA inserted into an immunogenic loop in influenza virus hemagglutinin can elicit IIIB, MN and RF neutralizing sera in immunized mice. Muster *et al.* [1994] (**vaccine antigen design**)
- 2F5: Broadly reactive neutralizing activity, ELDKWA is relatively conserved – neutralized 2 primary isolates. Purtscher *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 2F5: gp41 mutation (582 A/T) that reduces neutralization of anti-CD4 binding site MAbs does not alter 2F5's ability to neutralize. Thali *et al.* [1994]
- 2F5: Synergy with combinations of CD4-based molecules in inhibition of HIV-1 Env mediated cell fusion. Allaway *et al.* [1993] (**antibody interactions**)
- 2F5: Called IAM-41-2F5 – reports MAb to be IgG1 – the gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to conformationally sensitive neutralizing MAbs – neutralization efficiency of 2F5 is not affected. Klasse *et al.* [1993a] (**variant cross-recognition or cross-neutralization**)
- 2F5: DKWA defined as the core sequence – highly conserved epitope neutralizing MAb. Buchacher *et al.* [1992]; Muster *et al.* [1993] (**antibody binding site definition and exposure**)

No. 751

MAb ID Z13e1

**HXB2 Location** gp160 (666–677)**Author Location****Epitope** WASLWNWFDITN**Subtype** B**Neutralizing** P**Immunogen** HIV-1 infection**Species (Isotype)** human**Ab Type** gp41 MPER (membrane proximal external region)**Research Contact** Michael Zwick, The Scripps Research Institute, zwick@scripps.edu**References** Nelson *et al.* 2007**Keywords** antibody binding site definition and exposure, binding affinity, neutralization

- Z13e1: Z13e1, a high affinity variant of Fab Z13, was identified through targeted mutagenesis and affinity selection against gp41 and an MPER peptide. Z13e1 showed 100-fold improvement in binding affinity for MPER antigens over Z13, and improved neutralization potency against sensitive HIV-1. Alanine scanning revealed that N671 and D674 residues are crucial for peptide recognition and neutralization of HIV-1 by this Fab. Z13e1 was shown to bind with high affinity to an epitope overlapping those of 2F5 and 4E10 with the minimal epitope WASLWNWFDITN, indicating that the limited neutralization potency results from the limited access to the epitope within the envelope trimer. Nelson *et al.* [2007] (**antibody binding site definition and exposure, neutralization, binding affinity**)

No. 752

MAb ID 4E10

**HXB2 Location** gp160 (671–676)**Author Location** gp160 (671–676 MN)**Epitope** NWFDIT**Neutralizing** P**Immunogen** HIV-1 infection**Species (Isotype)** human (IgG3κ)**Ab Type** C-term, gp41 MPER (membrane proximal external region)**Research Contact** Herman Katinger, Inst. Appl. Microbiol. University of Agricultural Science, Vienna, Austria, or Polymun Scientific Inc.,**References** Gray *et al.* 2006; Joos *et al.* 2006; Cham *et al.* 2006; Choudhry *et al.* 2006; Holl *et al.* 2006a; Hager-Braun *et al.* 2006; Brunel *et al.* 2006; Quakkelaar *et al.* 2007; Nelson *et al.* 2007; Law *et al.* 2007; Kothe *et al.* 2007; Ferrantelli *et al.* 2007; Dimitrov *et al.* 2007; Dhillon *et al.* 2007; Dey *et al.* 2007; Choudhry *et al.* 2007; Cardoso *et al.* 2007; Brown *et al.* 2007; Blish *et al.* 2007; Alam *et al.* 2007; Luo *et al.* 2006; Liao *et al.* 2006; Holl *et al.* 2006b; Haynes & Montefiori 2006; Dong & Chen 2006; Alving *et al.* 2006; Zwick *et al.* 2005; Raviv *et al.* 2005; Nakowitsch *et al.* 2005; Haynes *et al.* 2005; Cardoso *et al.* 2005; Safrit *et al.* 2004; Pughach *et al.* 2004; Opalka *et al.* 2004; Ferrantelli *et al.* 2004a; Ferrantelli *et al.* 2004b; Binley *et al.* 2004; Gorny & Zolla-Pazner



2004; Kitabwalla *et al.* 2003; Wang 2003; Fiebig *et al.* 2003; Ferrantelli *et al.* 2003; Binley *et al.* 2003; Ferrantelli & Ruprecht 2002; Xu *et al.* 2002; Xu *et al.* 2001; Zwick *et al.* 2001c; Zwick *et al.* 2001b; Stiegler *et al.* 2001; D'Souza *et al.* 1994; Buchacher *et al.* 1994; Buchacher *et al.* 1992

**Keywords** acute/early infection, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, binding affinity, co-receptor, dendritic cells, escape, immunoprophylaxis, immunotherapy, kinetics, mimics, mother-to-infant transmission, neutralization, optimal epitope, responses in children, review, structure, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization, viral fitness and reversion

- 4E10: The autoantibody nature of the two membrane proximal HIV-1 neutralizing antibodies, 2F5 and 4E10, was evaluated by comparison to human anti-cardiolipin mAbs derived from a primary antiphospholipid syndrome patient. Both 2F5 and 4E10 bound specifically to cardiolipin. CDR3 sequence similarities between 2F5, 4E10 and anti-cardiolipin mAbs were observed. A difference in the binding mode of both 2F5 and 4E10 when binding to peptide in solution versus peptide conjugated to lipids was observed, in that binding to the peptide-lipid conjugate was best fit by a two step conformational change model. These results suggest that these antibodies share binding and structural similarities with human autoantibodies and their induction by vaccines or natural infection therefore might be limited by immune tolerance mechanisms. Alam *et al.* [2007] (**kinetics, antibody sequence variable domain**)
- 4E10: 7/15 and 9/15 subtype A HIV-1 envelopes from samples taken early in infection were neutralized by MAbs 4E10 and 2F5, respectively, and the potency was generally modest. Mutational patterns in the MAb binding sites did not readily explain the observed patterns of sensitivity and resistance. Blish *et al.* [2007] (**neutralization, variant cross-recognition or cross-neutralization, acute/early infection, subtype comparisons**)
- 4E10: This study confirmed binding of 4E10 to cardiolipin (CL) and showed that this Ab also binds to phosphatidylinositol phosphate (PIP). Binding of 4E10 to CL and PIP was inhibited by phosphocoline and enhanced by inositol (PIP only). Anti-PIP mouse monoclonal antibodies had neutralizing antibodies against 2 HIV primary isolates. Brown *et al.* [2007] (**mimics, neutralization, binding affinity**)
- 4E10: Structural effects of both increasing peptide length and introducing helix-promoting constraints in the 4E10 epitope were investigated. Helical constraints increased binding affinity of the peptide epitope for 4E10 by increasing the stability of the complex and allowing interaction with an additional helical turn including Leu679 and Trp680. Crystal structures of the 4E10 bound to peptide epitopes revealed that the gp140 residues Trp672, Phe673, Ile675, Thr676 Leu679 and Trp680 have the most significant contact with the antibody, and the core motif was redefined as: WFX(I/L)(T/S)XX(L/I)W. Cardoso *et al.* [2007] (**antibody binding site definition and exposure, vaccine antigen design, structure**)
- 4E10: 2F5, 4E10, and m46 neutralization was more potent when tested in a HeLa cell line expressing low CCR5 than in a HeLa cell line expressing high CCR5 levels. PBMC tend to have low CCR5 expression. Choudhry *et al.* [2007] (**neutralization, assay standardization/improvement**)
- 4E10: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP trimers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. Dey *et al.* [2007] (**vaccine antigen design**)
- 4E10: Chimeric SIV viruses containing 2F5 and 4E10 epitopes were not neutralized by the broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals, indicating that MPER NAb epitopes did not account for the broad neutralizing activity observed. Dhillion *et al.* [2007] (**antibody binding site definition and exposure, neutralization**)
- 4E10: Kinetics experiments of 4E10 binding to MPER region during viral fusion showed that the 4E10 kinetics resembled those of the six-helix bundle formation and fusion blocker C34, indicating that the function of MPER in the fusion cascade is still in effect at a late stage in the fusion reaction. Binding of 4E10 was shown to decrease upon triggering HIV-1 Env-expressing cells with appropriate target cells and addition of C34 did not counteract this loss, suggesting that changes in exposure of MPER occur independently of the six-helix bundle formation. Dimitrov *et al.* [2007] (**antibody binding site definition and exposure, neutralization, kinetics, binding affinity**)
- 4E10: Newborn macaques were challenged orally with the highly pathogenic SHIV89.6P and then treated intravenously with a combination of IgG1b12, 2G12, 2F5 and 4E10 one and 12 hours post-virus exposure. All control animals became highly viremic and developed AIDS. In the group treated with mAbs 1 hour post-virus exposure, 3/4 animals were protected from persistent systemic infection and one was protected from disease. In the group treated with mAbs 12 hour post-virus exposure, one animal was protected from persistent systemic infection and disease was prevented or delayed in two animals. IgG1b12, 2G12, and 4E10 were also given 24 hours after exposure in a separate study; 4/4 treated animals become viremic, but with delayed and lower peak viremia relative to controls. 3/4 treated animals did not get AIDS during the follow up period, and 1 showed a delayed progression to AIDS, while the 4 untreated animals died of AIDS. Thus the success of passive immunization with NAb depends on the time

window between virus exposure and the start of immunoprophylaxis. Ferrantelli *et al.* [2007] (**immunoprophylaxis**)

- 4E10: Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 co-receptor. Primary isolate Envs varied between completely resistant or somewhat sensitive to neutralization by membrane proximal Nabs 4E10 and 2F5. The most sensitive Con B construct was the truncated version of Con B Env with a stop codon immediately following the membrane spanning domain, suggesting that truncation of the gp41 cytoplasmic domain facilitates greater accessibility of the MPER region. The Con B gp160 was quite resistant, and the gp160-201N/S more sensitive, to 4E10 and 2F5. Kothe *et al.* [2007] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)
- 4E10: High levels of gp120-specific Abs were elicited when mice and rabbits were immunized by DNA priming and protein boosting with G1 and G2 grafts, consisting of 2F5 and 4E10, and 4E10 epitopes, respectively, engrafted into the V1/V2 region of gp120. A consistent NAb response against the homologous JR-FL virus was detected in rabbits but not in mice. 4E10 bound to the engrafted construct, but embedding the MPER epitopes in the immunogenic V1/V2 region did not result in eliciting anti-MPER antibodies in mice or rabbits. 4E10 binding to G2 was greater than to G1, and could be enhanced by deletion of one or two amino acid residues immediately preceding the 4E10 epitope, presumably due to rotation of the epitope along the alpha-helix in the engrafted region. Law *et al.* [2007] (**vaccine antigen design**)
- 4E10: Z13e1, a high affinity variant of Fab Z13, was identified through targeted mutagenesis and affinity selection against gp41 and an MPER peptide. Z13e1 showed 100-fold improvement in binding affinity for MPER antigens over Z13, but was still less potent than 4E10 at neutralizing several pseudotyped Envs. 4E10 was found to be less effective inhibitor of biotinylated Z13e1 than the other way around. Neutralization assays of HIV-1 JR2 MPER alanine mutants showed that mutants W666A and W672A were completely resistant to neutralization by 4E10. In contrast to a previous publication, it was also found that neutralization of HIV-1 JR-FL by 4E10 was not greatly improved in going from the Fab to IgG format. Nelson *et al.* [2007] (**antibody binding site definition and exposure**)
- 4E10: This study found that, contrary to expectations, the viruses resistant to b12, 4E10, 2G12 and 2F5 neutralization did not have lower replication kinetics than viruses sensitive to neutralization. Viruses from early infection tended to have relatively low replications rates. Quakkelaar *et al.* [2007] (**neutralization, viral fitness and reversion, escape**)
- 4E10: This review summarizes current knowledge of HIV-1 lipid-protein interactions and antibodies to liposomal phospholipids and cholesterol. A potential use of Abs to lipids to neutralize HIV-1 and a potential role of the broadly neutralizing HIV-1 Abs, mainly 2F5 and 4E10, in binding to phospholipids is discussed. Alving *et al.* [2006] (**antibody binding site definition and exposure, neutralization, review**)
- 4E10: The optimal length of the 4E10 epitope was determined to the gp41 residues 671 to 683. Several residues in the epitope were shown to be essential for 4E10 recognition (W672, F673 and T676) and five more were shown to make significant contributions to 4E10 binding (N671, D674, I675, W680 and L679). When helix-promoting residues and helix-inducing tethers were incorporated, several peptides showed improved affinity over the starting peptide suggesting that they may be more likely to elicit 4E10-like neutralizing Abs. Brunel *et al.* [2006] (**optimal epitope, kinetics, binding affinity, structure**)
- 4E10: The majority of broadly cross-reactive neutralizing (BCN) Envs were neutralized at lower concentrations of 4E10 than the non-BCN Envs. Amino acid variability of the 4E10 epitope was examined. The presence of T at position 662 was associated with increased sensitivity to neutralization by this Ab. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, escape, subtype comparisons**)
- 4E10: Neutralization of HIV-1 primary isolates of different HIV-1 clades (A, B, C, D, E) by 4E10 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of 4E10 in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor, neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 4E10: Genetic variability and co-variation of the mAb 2F5, 4E10 and Z13 epitopes in B and non B clades was investigated. A significant shift in the predominant sequence patterns over time was observed for all three epitopes. Also, significant inter-subtype genetic variability of the three epitopes was detected. However, the 4E10 epitope displayed a more similar variability within B clade and non-B clades, concurring with the cross-clade neutralizing activity of this mAb. Epitope co-variation was also noted, as one third of the recently isolated HIV-1 strains displayed simultaneous epitope variants. Dong & Chen [2006] (**antibody binding site definition and exposure, subtype comparisons**)
- 4E10: Env-pseudotyped viruses were constructed from the gp160 envelope genes from seven children infected with subtype C HIV-1. 4E10 alone or in combination with IgG1b12, 2G12 and 2F5 neutralized all of the seven viruses. Gray *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, responses in children, mother-to-infant transmission**)
- 4E10: The antigenic determinants recognized by 4E10 were characterized using recombinant glycosylated full-length Ags, and nonglycosylated and truncated Ags. This Ab recognized three peptides located at the N-terminal region of gp120 and gp41, respectively. It is suggested that 4E10 binds to the fusogenic peptide of gp41 and the N-terminal region of gp120, inhibiting insertion of fusogenic peptide into the host cell membrane. Hager-Braun *et al.* [2006] (**antibody binding site definition and exposure, optimal epitope, variant cross-recognition or cross-neutralization, binding affinity**)

- 4E10: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure, neutralization, optimal epitope, escape, review, subtype comparisons, structure**)
- 4E10: Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in iMDDCs was evaluated. The HIV-neutralizing activity of 4E10 was observed to be higher in iMDDCs than in PHA-stimulated PBMCs using both HIV-1 Bx08 and BaL. Holl *et al.* [2006b] (**neutralization, dendritic cells**)
- 4E10: The ability of this Ab to inhibit viral growth was increased when macrophages and immature dendritic cells (iDCs) were used as target cells instead of PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**dendritic cells**)
- 4E10: Pharmacokinetic properties of this Ab were studied in HIV infected patients infused with high doses of 4E10. The Ab did not elicit an endogenous immune response and had distribution and systemic clearance values similar to other Abs. The elimination half-life was measured to 5.5 days. Joos *et al.* [2006] (**kinetics, immunotherapy**)
- 4E10: The gp140δCFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. 4E10 was shown to bind specifically to CON6, CON-S and subtype B recombinant proteins but not to subtype A and C recombinant proteins or to the two subtype B gp120 proteins. The specific binding of 4E10 to CON-S indicated that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure, vaccine antigen design, subtype comparisons**)
- 4E10: gp41 and p15E of the porcine endogenous retrovirus (PERV) share structural and functional similarities, and epitopes in the membrane proximal region of p15E are able to elicit NAbs upon immunization with soluble p15E. Rabbits immunized with a VSV recombinant expressing an HIV-1 membrane-proximal external region (MPER) fused to PERV p15E, with a fusion p15E-HIV MPER protein boost, elicited HIV specific NAbs. The MPER contains the 4E10 epitope. Luo *et al.* [2006] (**vaccine antigen design**)
- 4E10: The crystal structure of 4E10 complexed with a 13 aa peptide (KGWNWFDITNWK) that contains the NWFDT binding site was resolved to 2.2 Å resolution. 4E10 has a canonical beta sandwich Ig-fold, with H3/H2 loop hydrophobicity and a long CDR H3 loop that mediates C-terminal base and central amino acid interactions; it extends beyond the peptide and its orientation suggests it could potentially allow hydrophobic contacts with the viral membrane. 4E10 complex formation induces a conformational change in the peptide such that it forms an amphipathic alpha-helix with a hydrophobic face that interacts with 4E10, with Trp672 primary, and Phe673, Ile675 and Thr676 secondary, contact points. Cardoso *et al.* [2005] (**structure**)
- 4E10: 2F5 and 4E10 both bind to membrane proximal regions of gp41, and have long hydrophobic CDR3 regions characteristic of polyspecific autoreactive antibodies. Of 35 Env-specific MAbs tested, only 2F5 and 4E10 were found to be reactive with phospholipid cardiolipin. Vaccine induction of antibodies that react with these gp41 membrane proximal regions may be rare because of elimination due to autoantigen mimicry. 4E10 also reacted with systemic lupus erythematosus (SLE) autoantigen SS-A/Ro, and both 4E10 and 2F5 reacted with HEp-2 cells with diffuse cytoplasmic and nuclear patterns indicating polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)
- 4E10: Passive immunization of 8 HIV-1 infected patients with 4E10, 2F5 and 2G12 (day 0, 4E10; days 7, 14 and 21 4E10+2G12+2F5; virus isolated on days 0 and 77) resulted in 0/8 patients with virus that escaped all three NAbs. No viruses escaped 4E10, but only one virus in one patient had the NWFDT epitope sequence; the W, F and I were conserved in all patients but the other amino acids varied both before and after treatment. A patient carrying the epitope sequence nwfSit had the least 4E10 sensitive virus. In a companion in vitro study, resistance to a single MAb emerged in 3-22 weeks, but triple combination resistance was slower and characterized by decreased viral fitness. In the core of the 4E10 epitope, NWFDT, 5/11 cases had a T->I escape; 2/11 had a F->L change; and 2/11 had substantial deletions, of WNWF overlapping, or NLWYI adjacent to the epitope. The lack of resistance to the combination of MAbs in vivo and the reduced fitness of the escape mutants selected in vitro suggests passive immunotherapy may be of value in HIV infection. Nakowitsch *et al.* [2005] (**escape, immunotherapy**)
- 4E10: Retrovirus inactivation for vaccine antigen delivery was explored through lipid modification by hydrophobic photoinduced alkylating probe 1.5 iodonaphthylazide (INA). The viral proteins were shown to be structurally intact in the treated non-infectious virus, through the preservation of antibody binding sites for polyclonal anti-gp120 serum, and for broadly neutralizing MAbs 2G12, b12 and 4E10, although the modifications of the lipid disabled viral infection. Raviv *et al.* [2005] (**vaccine antigen design**)
- 4E10: Alanine scanning mutations of the 21 amino acid region between positions 660-680 showed only 3 substitutions that reduced 4E10 binding, positions 1leldkwanlwnWFdisnwlW. No single Ala mutation was resistant to both 2F4 and 4E10. Ala substitutions in 11/20 positions enhanced neutralization sensitivity, LLeLdkWanLWNwfdIsNWLw. For peptides T20 and 4E10 neutralization was synergistic. Zwick *et al.* [2005] (**antibody binding site definition and exposure, escape**)
- 4E10: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. 4E10 was the most cross-reactive, moderately reactive in all 93 viruses tested from each subtype. WFXI was defined as the core motif, and this core is highly conserved in all M

group gp41 sequences. How potent the neutralizing activity is is somewhat context dependent. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

- 4E10; Neonatal rhesus macaques were exposed orally to a pathogenic SHIV, 89.6P. 4/8 were given an intramuscular, passive immunization consisting of NAbS 2G12, 2F5 and 4E10, each given at a different body sites at 40 mg/kg per Ab, at one hour and again at 8 days after exposure to 89.6P. The four animals that were untreated all died with a mean survival time of 5.5 weeks, the four animals that got the NAb combination were protected from infection. This model suggests antibodies may be protective against mother-to-infant transmission of HIV. Ferrantelli *et al.* [2004b] (**mother-to-infant transmission**)
- 4E10: Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. IgG1b12 could neutralize some O group strains when used on its own, and quadruple combination of b12, 2F5, 2G12, and 4E10, could neutralize the six Group O viruses tested between 62-97%. The linear epitope, NWFDT, of 4E10 is conserved in 3/6 group O strains. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)
- 4E10: This paper reviews MAbs that bind to HIV-1 Env. 4E10 binds to a region of gp41 proximal to cluster II (aa 662-676), neighboring the binding site of the broadly neutralizing MAb 2F5 and overlapping the epitope of neutralizing Fab Z13. 4E10 is the most broadly neutralizing MAb, neutralizing primary isolates from clades A, B, C, D, and CRF01 (E), although not the most potent. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 4E10: An antigen panel representing different regions of gp41 was generated, and sera from 23 individuals were screened. Anti-gp41 titers were very high, and sera bound to many regions of gp41, there were no immunologically silent regions. Many individuals had broad responses to diverse regions. High titer responses tended to focus on the N-heptad, C-heptad and 2F5-4E10 regions, but there was no correlation between neutralization capacity of sera and the particular peptides recognized. 4E10 responded to the three antigens that carried the minimal NWFNIT epitope, but was conformation and context sensitive. Opalka *et al.* [2004] (**assay development, assay standardization/improvement**)
- 4E10: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to Fab b12 and sCD4 that was attributed to changes in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. The IC50 for 4E10 was greater than 50 for CCcon19, and was 44 for CC1/85, so the primary virus was weakly neutralized by 4E10. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization, viral fitness and reversion**)
- 4E10: This review discusses research presented at the Ghent Workshop of prevention of breast milk transmission and immunoprophylaxis for HIV-1 in pediatrics (Seattle, Oct. 2002), and makes the case for developing passive or active immunoprophylaxis in neonates to prevent mother-to-infant transmission. Macaque studies have shown that passive transfer of NAb combinations (for example, IgG1b12, 2G12, 2F5, and 4E10) can confer partial or complete protection to infant macaques from subsequent oral SHIV challenge. Safrit *et al.* [2004] (**immunoprophylaxis, mother-to-infant transmission**)
- 4E10: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. gp41 NAbS 2F5 and 4E10 are able to potently neutralize the SOS pseudovirion post-attachment. Binley *et al.* [2003] (**vaccine antigen design**)
- 4E10: Four newborn macaques were challenged with pathogenic SHIV 89.6 and given post exposure prophylaxis using a combination of NAbS 2F5, 2G12, 4E10 and IgG1b12. 2/4 treated animals did not show signs of infection, and 2/4 macaques maintained normal CD4+ T cell counts and had a lower delayed peak viremia compared to the controls. Ferrantelli *et al.* [2003] (**antibody interactions, immunoprophylaxis, mother-to-infant transmission**)
- 4E10: Porcine endogenous retroviruses (PERVS) are a concern in the context of porcine xenotransplantation into humans; possible strategies for protection include PERV knock-out animals or vaccines. Goats immunized with the PERV transmembrane protein revealed two NAb epitope, E1 and E2. E2's epitope (FEGWFN) binds to a sequence that is perfectly preserved in all PERVS and highly conserved in all gammaretroviruses: MuLV carries FEGLFN, FeLV FEGWFN, and it shares three amino acids with the core epitope for the anti-HIV human neutralizing MAb 4E10, (LWNWFN). Fiebig *et al.* [2003]
- 4E10: MAbs IgG1b12, 2G12, 2F5 and 4E10 were tested for their ability to neutralize two primary HIV-1 clade A isolates (UG/92/031 and UG/92/037) and two primary HIV-1 clade D isolates (UG/92/001 and UG/92/005). 4E10 demonstrated the most potent cross-neutralization activity. Quadruple administration of MAbs IgG1b12, 2G12, 2F5, and 4E10 induced strong synergistic neutralization of 4 clade A isolates (UG/92/031, UG/92/037, RW/92/020 and RW/92/025) as well as 5 clade D isolates (UG/92/001,UG/9/005, /93/086/RUG/94/108, UG/94/114). The authors note this combination of 4 MAbs neutralizes primary HIV A, B, C, and D isolates. Kitabwalla *et al.* [2003] (**antibody interactions, immunoprophylaxis, variant cross-recognition or cross-neutralization, mother-to-infant transmission, subtype comparisons**)
- 4E10: Review of current neutralizing antibody-based HIV vaccine candidates and strategies of vaccine design. Strategies for targeting of the epitopes for NAbS 2F5, 2G12, 4E10,

- b12, and Z13 are described. Wang [2003] (**vaccine antigen design, review**)
- 4E10: Review of NAbs illustrating gp41's conformational change and exposure of the 4E10/Z13 epitope in the transient pre-hairpin form. Ferrantelli & Ruprecht [2002] (**antibody binding site definition and exposure**)
  - 4E10: Passive immunization of neonate macaques with a combination of F105+2G12+2F5 conferred complete protection against oral challenge with SHIV-vpu+ —the combination b12+2G12+2F5 conferred partial protection against SHIV89.6—such combinations may be useful for prophylaxis at birth and against milk born transmission—the synergistic combination of IgG1b12, 2G12, 2F5, and 4E10 neutralized a collection of HIV clade C primary isolates. Xu *et al.* [2002] (**antibody interactions, immunoprophylaxis, subtype comparisons**)
  - 4E10: 4E10 binds proximal to 2F5 and neutralizes primary isolates of clades A, B, C, D, and E. Viruses that were resistant to 2F5 were neutralized by 4E10 and vice versa. Stiegler *et al.* [2001] (**antibody binding site definition and exposure**)
  - 4E10: Twenty HIV clade C isolates from five different countries were susceptible to neutralization by anti-clade B MAbs in a synergistic quadruple combination of mAbs IgG1b12, 2G12, 2F5, and 4E10. Xu *et al.* [2001] (**antibody interactions, subtype comparisons**)
  - 4E10: MAbs 4E10 and Z13 both bind proximally to 2F5 to a conserved linear epitope that has some conformational aspects – both bind to MN virions, bind weakly to infected cells in a manner that is not disrupted by sCD4 and neutralize some primary isolates from clades B, C, and E – maps minimal 4E10 epitope to NWFDIT, contrary to an earlier report – different strains were refractive to neutralization by broadly neutralizing Abs IgG1b12, 2F5, Z13 and 4E10. Zwick *et al.* [2001b] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 4E10: Neutralization synergy between anti-HIV NAbs b12, 2G12, 2F5, and 4E10 was studied – a classic fixed-ratio method was used, as well as a method where one Ab was fixed at a low neutralization titer and the other was varied – using primary isolates, a two-four fold enhancement of neutralization was observed with MAb pairs, and a ten-fold enhancement with a quadruple Ab combination – no synergy was observed with any MAb pair in the neutralization of TCLA strain HXB2. Zwick *et al.* [2001c] (**antibody interactions**)
  - 4E10: MAbs generated by hybridoma, electrofusion of PBL from HIV-1 + volunteers with CB-F7 heteromyeloma cells – also binds to MHC class II proteins – anti-class II Abs are only found in HIV-1 positive people – this paper maps 4E10's binding site to AEGTDRV, gp160(823-829), but the later Zwick *et al.* study in 2001 revised the epitope location. Buchacher *et al.* [1994] (**antibody binding site definition and exposure, antibody generation**)
  - 4E10: Included in a multi-lab study for antibody characterization, binding and neutralization assay comparison. D'Souza *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- No. 753  
MAb ID Z13  
HXB2 Location gp160 (671–676)
- Author Location** gp41 (671–676 MN)  
**Epitope** NWFDIT  
**Subtype** B  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** C-term, gp41 MPER (membrane proximal external region)
- References** Cham *et al.* 2006; Nelson *et al.* 2007; Luo *et al.* 2006; Dong & Chen 2006; Gorny & Zolla-Pazner 2004; Wang 2003; Ferrantelli & Ruprecht 2002; Zwick *et al.* 2001b
- Keywords** antibody binding site definition and exposure, antibody generation, neutralization, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization
- Z13: Z13e1, a high affinity variant of Fab Z13, was identified through targeted mutagenesis and affinity selection against gp41 and an MPER peptide. Z13e1 showed 100-fold improvement in binding affinity for MPER antigens over Z13, and improved neutralization potency against sensitive HIV-1. Alanine scanning revealed that N671 and D674 residues are crucial for peptide recognition and neutralization of HIV-1 by this Fab. Z13e1 was shown to bind with high affinity to an epitope overlapping those of 2F5 and 4E10 with the minimal epitope WASLWNWFDITN, indicating that the limited neutralization potency results from the limited access to the epitope within the envelope trimer. Nelson *et al.* [2007] (**variant cross-recognition or cross-neutralization**)
  - Z13: This Ab was shown to infrequently neutralize cloned Envs (clades A, B, C, D, F1, CRF01\_AE, CRF02\_AG, CRF06\_cpx and CRF11\_cpx) derived from donors with and without broadly cross-reactive neutralizing antibodies. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
  - Z13: Genetic variability and co-variation of the mAb 2F5, 4E10 and Z13 epitopes in B and non B clades was investigated. A significant shift in the predominant sequence patterns over time was observed for all three epitopes. Also, significant inter-subtype genetic variability of the three epitopes was detected. However, the 4E10 epitope displayed a more similar variability within B clade and non-B clades, concurring with the cross-clade neutralizing activity of this mAb. Epitope co-variation was also noted, as one third of the recently isolated HIV-1 strains displayed simultaneous epitope variants. Dong & Chen [2006] (**antibody binding site definition and exposure, subtype comparisons**)
  - Z13:gp41 and p15E of the porcine endogenous retrovirus (PERV) share structural and functional similarities, and epitopes in the membrane proximal region of p15E are able to elicit NAbs upon immunization with soluble p15E. Rabbits immunized with a VSV recombinant expressing an HIV-1 membrane-proximal external region (MPER) fused to PERV p15E, with a fusion p15E-HIV MPER protein boost, elicited HIV specific NAbs. The MPER contains the Z13 epitope. Luo *et al.* [2006] (**vaccine antigen design**)
  - Z13: This paper reviews MAbs and Fabs that bind to HIV-1 Env. Z13 binds to a region of gp41 proximal to cluster II (aa

662-676), neighboring the binding site of the broadly neutralizing MAb 2F5 and overlapping the epitope of neutralizing MAb 4E10. Z13 is broadly neutralizing, neutralizing primary isolates from clades A, B, C, D and CRF01 (E). Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, review**)

- Z13: Review of current neutralizing antibody-based HIV vaccine candidates and strategies of vaccine design. Strategies for targeting of the epitopes for NAb 2F5, 2G12, 4E10, b12, and Z13 are described. Wang [2003] (**vaccine antigen design, review**)
- Z13: Review of NAb that notes Z13 is a phage display generated FAb fragment from a B clade infected individual and that illustrates gp41's conformational change and exposure of the 4E10/Z13 epitope in the transient pre-hairpin form. Ferrantelli & Ruprecht [2002] (**antibody binding site definition and exposure, antibody generation**)
- Z13: MAb 4E10 and FAb Z13 both bind proximally to 2F5 to a relatively conserved linear epitope that has some conformational aspects – both bind to MN virions, bind weakly to infected cells in a manner that is not disrupted by sCD4 and can neutralize some primary isolates from clades B, C, and E – Z13 was selected using a phage display library with the MN gp41 peptide LLELDKWASLWNWFDITNWSW from an HIV infected donor who had an exceptionally broad NAb response – different strains were refractive to neutralization by broadly neutralizing Abs IgG1b12, 2F5, Z13 and 4E10 – epitope location noted here is by analogy to MAb 4E10. Zwick *et al.* [2001b] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization**)

No. 754

MAb ID B30

HXB2 Location gp160 (720–734)

Author Location gp41 (720–734 BH10)

Epitope HLPIPRGPDRPEGIE

Neutralizing

Immunogen vaccine

Vector/Type: protein Strain: B clade LAI

HIV component: gp160

Species (Isotype) mouse (IgG1)

Research Contact George Lewis

References Abacioglu *et al.* 1994

- B30: Epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

No. 755

MAb ID polyclonal

HXB2 Location gp160 (724–745)

Author Location gp41 (731–752)

Epitope PRGPDRPEGIEEGGERDRDRS

Neutralizing

Immunogen vaccine

Vector/Type: Cowpea mosaic virus Strain:

B clade IIIB HIV component: gp41

Species (Isotype) mouse (IgA, IgG2a)

References Durrani *et al.* 1998

- Comparison of intranasal and oral immunization of HIV-1 peptide expressed in a plant viral vector – intranasal gave the better response. Durrani *et al.* [1998]

No. 756

MAb ID 41S-2

HXB2 Location gp160 (725–745)

Author Location gp160 (732–750)

Epitope RGPDRPEGIEEGGERDRDRS

Neutralizing yes

Immunogen vaccine

Vector/Type: peptide keyhole limpet hemo-cyanin (KLH) conjugate HIV component: gp41

Species (Isotype) mouse (IgG2bk)

References Hifumi *et al.* 2003; Hifumi *et al.* 2002; Hifumi *et al.* 2000b; Hifumi *et al.* 2000a

Keywords anti-idiotypic, antibody sequence variable domain

- 41S-2: A murine Ab called i41SL1-2 was raised against the complementary determining region of the 41S-2 light chain, CRDL-1 (RSSKSLLYSNGNTYLY). As with 41S-2-L, the light chain of i41SL1-2 also had catalytic activity and degraded the immunizing peptide, initially cleaving between the Arg1 and Ser2. i41SL1-2 did not cross-react with gp41 peptide, gp120 V3 loop peptide and bound weakly to 41S-2-L. i41SL1-2 shows homology to the anti-VIP Ab (VIP, vasoactive intestinal peptide) that also has peptidase character. Both light chains contain a catalytic triad composed of Asp, Ser, and His (for i41SL1-2: Asp73, Ser 76 or Ser70 and His 79). Intact i41SL1-2 was unable to degrade CDRL-1, possibly due to an immobile inactive conformation of the catalytic triad. Hifumi *et al.* [2003] (**anti-idiotypic, antibody sequence variable domain**)
- 41S-2: 41S-2-L refers to the light chain of 41S-2, which can enzymatically decompose the gp41 protein of HIV-1, but doesn't degrade unreacted proteins. The peptide RGPDRPEGIEEGGERDRDRS, against which the MAb was raised, can also be cleaved, initially between Glu12-Gly13, followed by successive cleavage reactions. Hifumi *et al.* [2002]
- 41S-2: BALBc mice were immunized with gp41 peptide and a MAb specific for the peptide was generated – isolated MAb light chains displayed proteolytic activity toward the peptide epitope which may be due to a catalytic triad on light chain (Asp73, Ser76, and His79) – no catalytic activity was observed for the whole antibody. Hifumi *et al.* [2000a]
- 41S-2: The complementary determining region of 41S-2-L, the light chain of 41S-2, is strongly involved in gp41 recognition. This light chain can serve as a molecular catalyst for gp41 degradation. Hifumi *et al.* [2000b]

No. 757

MAb ID C8

HXB2 Location gp160 (727–732)

Author Location gp41 (727–732 BH10)

Epitope PDRPEG

Subtype B

Neutralizing no

Immunogen vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG1)

**Ab Type** C-term

**References** Heap *et al.* 2005a; Dimmock 2005; McLain *et al.* 2001; Abacioglu *et al.* 1994; Pincus *et al.* 1993; Pincus & McClure 1993

**Keywords** review

- C8: This review summarizes the complex antigenic properties of an external loop in the gp41 tail (spanning the Kennedy sequence), highlighting specific MAbs. C8 binds to the epitope PDRPEG and does not neutralize virus. Dimmock [2005] (**review**)
- C8: Unlike SAR1, a MAb that binds near the C8 epitope within the Kennedy peptide, C8 cannot inhibit fusion between HIV-1 infected and target cells. C8 recognizes PDRPEG on the surface of HIV-1 infected cells, but not on virions and is non-neutralizing. Heap *et al.* [2005a]
- C8: The substitution 725 RG (P[R->G]GPDRPEGIEEEGGGERDRDRS) alters the antigenic exposure of this region on the virion resulting in the loss of the downstream neutralizing epitope ERDRD, increased exposure of the epitope GPDRPEG in the virion, while the epitope IEEE remains unchanged. McLain *et al.* [2001]
- C8: Epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]
- C8: Immunotoxin of C8 coupled to ricin-A does not mediate cells killing, and is not affected by sCD4. Pincus & McClure [1993]
- C8: Ab response in IIIB lab workers was compared to gp160 LAI vaccine recipients – C8 was used as a control – the dominant response among vaccinees was to this mid-gp41 region, but not among the infected lab workers – Abs binding this region do not neutralize, bind to infected cells, nor serve as immunotoxins. Pincus *et al.* [1993]

**No.** 758

**MAb ID** B31

**HXB2 Location** gp160 (727–734)

**Author Location** gp41 (727–734 BH10)

**Epitope** PDRPEGIE

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG1)

**References** Abacioglu *et al.* 1994

- B31: Epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]

**No.** 759

**MAb ID** B33

**HXB2 Location** gp160 (727–734)

**Author Location** gp41 (727–734 BH10)

**Epitope** PDRPEGIE

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* gp160

**Species (Isotype)** mouse (IgG1)

**References** Bristow *et al.* 1994; Abacioglu *et al.* 1994

- B33: Epitope boundaries mapped by peptide scanning IgG1. Abacioglu *et al.* [1994]
- B33: There are two MAbs in the literature named B33, see also gp120, positions 123–142 – MAb generated in a study of the humoral immune response to Baculovirus-expressed mis-folded rgp160 IIIB:NL43, MicroGenSys. Bristow *et al.* [1994]

**No.** 760

**MAb ID** 1576

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *Strain:* B clade IIIB  
*HIV component:* gp41

**Species (Isotype)** mouse

**References** Vella *et al.* 1993

- 1576: Not neutralizing. Vella *et al.* [1993]

**No.** 761

**MAb ID** 1578

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *Strain:* B clade IIIB  
*HIV component:* gp41

**Species (Isotype)** mouse

**References** Vella *et al.* 1993; Evans *et al.* 1989

- 1578: Core epitope: IEEE – in this study, neutralized IIIB, but not RF or MN. Vella *et al.* [1993]
- 1578: No neutralizing activity – epitope may be formed by regions from both poliovirus and HIV. Evans *et al.* [1989]

**No.** 762

**MAb ID** 1579

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *Strain:* B clade IIIB  
*HIV component:* gp41

**Species (Isotype)** mouse

**References** Vella *et al.* 1993

- 1579: Core epitope: IEEE – neutralized IIIB, but not RF or MN. Vella *et al.* [1993]

**No.** 763

**MAb ID** 1583

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *Strain:* B clade  
 IIIB *HIV component:* gp41  
**Species (Isotype)** mouse

**References** Heap *et al.* 2005a; Dimmock 2005; Sattentau *et al.* 1995; Vella *et al.* 1993; Evans *et al.* 1989

**Keywords** review

- 1583: This review summarizes the complex antigenic properties of an external loop in the gp41 tail (Kennedy sequence), highlighting specific MAbs. 1577 and 1583 bind to the epitope ERDRD and do not neutralize virus. Dimmock [2005] (review)
- 1583: Unlike SAR1, a MAb that binds near the 1583 epitope within the Kennedy peptide, 1583 cannot inhibit fusion between HIV-1 infected and target cells. 1583 and 1577 neutralize only in the presence of complement. Heap *et al.* [2005a]
- 1583: Suggested to bind to a cytoplasmic domain, epitope not exposed at the surface of HIV-1 infected cells. Sattentau *et al.* [1995]
- 1583: Core epitope: ERDRD – Could neutralize HIV IIIB but not HIV RF. Vella *et al.* [1993]
- 1583: Neutralizing activity, less broad than 1577. Evans *et al.* [1989]

**No.** 764

**MAb ID** 1899

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *Strain:* B clade  
 IIIB *HIV component:* gp41

**Species (Isotype)** mouse

**References** Vella *et al.* 1993

- 1899: Could neutralize HIV IIIB and HIV RF. Vella *et al.* [1993]

**No.** 765

**MAb ID** 1907

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *Strain:* B clade  
 IIIB *HIV component:* gp41

**Species (Isotype)** mouse

**References** Vella *et al.* 1993

- 1907: Could not neutralize HIV IIIB, RF or MN. Vella *et al.* [1993]

**No.** 766

**MAb ID** 1908

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *Strain:* B clade  
 IIIB *HIV component:* gp41

**Species (Isotype)** mouse

**References** Sattentau *et al.* 1995; Vella *et al.* 1993; Evans *et al.* 1989

- 1908: Cytoplasmic domain, epitope not exposed at the surface of HIV-1 infected cells. Sattentau *et al.* [1995]
- 1908: Neutralized IIIB, but not RF or MN. Vella *et al.* [1993]

**No.** 767

**MAb ID** 1909

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *Strain:* B clade  
 IIIB *HIV component:* gp41

**Species (Isotype)** mouse

**References** Vella *et al.* 1993

- 1909: Neutralized HIV IIIB but not HIV RF. Vella *et al.* [1993]

**No.** 768

**MAb ID** 41-1

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB  
*HIV component:* gp41

**Species (Isotype)** mouse (IgMκ)

**References** Dalgleish *et al.* 1988; Mani *et al.* 1994

- 41-1: This antibody gp41(735-752 IIIB) Dalgleish *et al.* [1988] seems to have been named the same as a different MAb to gp41(584-609) Mani *et al.* [1994]. Dalgleish *et al.* [1988]; Mani *et al.* [1994]
- 41-1: Neutralizes HIV-1 but not HIV-2 strains. Dalgleish *et al.* [1988]

**No.** 769

**MAb ID** 41-2

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade IIIB  
*HIV component:* gp41

**Species (Isotype)** mouse (IgMκ)

**References** Dalgleish *et al.* 1988

- 41-2: Neutralizes HIV-1 but not HIV-2 strains. Dalgleish *et al.* [1988]

**No.** 770

**MAb ID** 41-3

**HXB2 Location** gp160 (728–745)

**Author Location** gp41 (735–752 IIIB)

**Epitope** DRPEGIEEEGGGERDRDRS



- Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade IIIB  
*HIV component:* gp41
- Species (Isotype)** mouse (IgMk)
- References** Dalgleish *et al.* 1988
- 41-3: Neutralizes HIV-1 but not HIV-2 strains. Dalgleish *et al.* [1988]
- No.** 771  
**MAb ID** ED6  
**HXB2 Location** gp160 (728–745)  
**Author Location** gp41 (735–752 IIIB)  
**Epitope** DRPEGIEEEGGGERDRRS  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)** mouse (IgM)  
**References** Evans *et al.* 1989
- No.** 772  
**MAb ID** LA9 (121-134)  
**HXB2 Location** gp160 (728–745)  
**Author Location** gp41 (735–752 IIIB)  
**Epitope** DRPEGIEEEGGGERDRRS  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)** mouse (IgM)  
**References** Evans *et al.* 1989
- No.** 773  
**MAb ID** 1575  
**HXB2 Location** gp160 (728–745)  
**Author Location** gp41 (735–752 IIIB)  
**Epitope** DRPEGIEEEGGGERDRRS  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* poliovirus *Strain:* B clade IIIB *HIV component:* gp41
- Species (Isotype)** mouse  
**Ab Type** C-term
- Research Contact** C. Vella, NIBSC, Potters Bar UK
- References** Heap *et al.* 2005a; Dimmock 2005; Cleveland *et al.* 2000a; Buratti *et al.* 1997; Vella *et al.* 1993; Evans *et al.* 1989
- Keywords** review
- 1575: This review summarizes the complex antigenic properties of an external loop in the gp41 tail (Kennedy sequence), highlighting specific MAbs. 1575 is noted to bind to the epitope IEEE and does not neutralize virus. Dimmock [2005] (review)
  - 1575: Unlike SAR1, a MAb that binds near the 1575 epitope within the Kennedy peptide, 1575 cannot inhibit fusion between HIV-1 infected and target cells. Heap *et al.* [2005a]
  - 1575: Ab binding to IEEE suppresses neutralizing Ab binding to adjacent epitope ERDRD. Cleveland *et al.* [2000a]
  - 1575: Study shows that MAb 1575 can recognize the IEEE sequence in both gp41, and in the HPG30 region of the p17 protein – motif is conserved in both regions in different HIV-1 clades. Buratti *et al.* [1997]
- 1575: Core epitope: IEEE – neutralized IIIB, but not RF or MN. Vella *et al.* [1993]
  - 1575: Neutralizing activity, less broad than 1577. Evans *et al.* [1989]
- No.** 774  
**MAb ID** 88-158/02  
**HXB2 Location** gp160 (732–747)  
**Author Location** gp41 (732–752 IIIB)  
**Epitope** GIEEEGGGERDRRSIR  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp41
- Species (Isotype)** mouse (IgG2b)
- References** Niedrig *et al.* 1992a
- 88-158/02: Mild inhibition of *in vitro* activity at high MAb concentrations – profound enhancing activity at low concentrations – significant reactivity to virion – domain non-immunogenic in humans. Niedrig *et al.* [1992a]
- No.** 775  
**MAb ID** 88-158/022  
**HXB2 Location** gp160 (732–747)  
**Author Location** gp41 (732–752 IIIB)  
**Epitope** GIEEEGGGERDRRSIR  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp41
- Species (Isotype)** mouse (IgG2b)
- References** Niedrig *et al.* 1992a
- 88-158/022: Mild inhibition of *in vitro* activity at high MAb concentrations – profound enhancing activity at low concentrations – significant reactivity to virion – domain non-immunogenic in humans. Niedrig *et al.* [1992a]
- No.** 776  
**MAb ID** 88-158/079  
**HXB2 Location** gp160 (732–747)  
**Author Location** gp41 (732–752 IIIB)  
**Epitope** GIEEEGGGERDRRSIR  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp41
- Species (Isotype)** mouse (IgG1)
- References** Niedrig *et al.* 1992a
- 88-158/079: Mild inhibition of HIV *in vitro* at high MAb concentrations – profound enhancing activity at low concentrations – weak binding to virion – domain non-immunogenic in humans. Niedrig *et al.* [1992a]
- No.** 777  
**MAb ID** polyclonal  
**HXB2 Location** gp160 (733–736)  
**Author Location** gp41 (735–752 IIIB)  
**Epitope** IEEE  
**Neutralizing** L  
**Immunogen** vaccine

*Vector/Type:* Cowpea mosaic virus *HIV component:* gp41

**Species (Isotype)** mouse (IgG)

**Ab Type** C-term

**References** McLain *et al.* 2001; Cleveland *et al.* 2000b

- The substitution 725 RG (P[R->G]GPDRPEGIEEEGGGERDRDRS) alters the antigenic exposure of this region on the virion resulting in the loss of the downstream neutralizing epitope ERDRD, increased exposure of the epitope GPDRPEG in the virion, while the epitope IEEE remains unchanged. McLain *et al.* [2001]
- When PRGPDRPEGIEEEGGGERDRDRS was used as antigen an immunodominant, non-neutralizing response to IEEE was observed, but immunization GERDRDR shifts the response to ERDRD. Cleveland *et al.* [2000b]

**No.** 778

**MAb ID** polyclonal

**HXB2 Location** gp160 (733–736)

**Author Location** gp41 (735–752 NL43)

**Epitope** IEEE

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* Cowpea mosaic virus *HIV component:* gp41

**Species (Isotype)** mouse (IgG)

**Ab Type** C-term

**References** McLain *et al.* 2001

- The substitution 725 RG (P[R->G]GPDRPEGIEEEGGGERDRDRS) alters the antigenic exposure of this region on the virion resulting in the loss of the downstream neutralizing epitope ERDRD, increased exposure of the epitope GPDRPEG in the virion, while the epitope IEEE remains unchanged. McLain *et al.* [2001]

**No.** 779

**MAb ID** B8

**HXB2 Location** gp160 (733–741)

**Author Location** gp41 (733–741 BH10)

**Epitope** IEEEGGERD

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade LAI *HIV component:* gp160

**Species (Isotype)** mouse (IgG1)

**References** Abacioglu *et al.* 1994; Pincus *et al.* 1993

- B8: Epitope boundaries mapped by peptide scanning. Abacioglu *et al.* [1994]
- B8: Ab response in IIIB lab workers was compared to gp160 LAI vaccine recipients – B8 was used as a control – the dominant response among vaccinees was to this mid-gp41 region, but not among the infected lab workers – Abs binding this region do not neutralize, bind to infected cells, nor serve as immunotoxins. Pincus *et al.* [1993]

**No.** 780

**MAb ID** SAR1

**HXB2 Location** gp160 (738–744)

**Author Location** gp41 (735–752 IIIB)

**Epitope** GERDRDR

**Subtype B**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* Cowpea mosaic virus *HIV component:* gp41

**Species (Isotype)** mouse (IgG2ak)

**Ab Type** C-term

**References** Heap *et al.* 2005a; Dimmock 2005

**Keywords** antibody binding site definition and exposure, review

- SAR1: This ERDRD-specific MAb recognizes an externalized loop of the gp41 C-terminal domain, and can reduce the yield of infectious progeny and inhibit fusion post-attachment, but not neutralize free virus. Dimmock [2005] (**review**)
- SAR1: This paper confirms the post-attachment neutralization (PAN) activity of this gp41 C-terminal tail-specific Ab – cell fusion between infected and uninfected cells is inhibited and is temperature dependent. This MAb does not neutralize free virus, and due to PAN activity, is considered to bind an epitope on the external surface of the membrane. The SAR1 epitope is exposed optimally after infected and non-infected cells have attached, prior to fusion. sCD4 binding does not enhance binding of SAR1. MAbs to adjacent epitopes do not have PAN activity. Heap *et al.* [2005a] (**antibody binding site definition and exposure**)

**No.** 781

**MAb ID** 1577

**HXB2 Location** gp160 (739–743)

**Author Location** gp41 (735–752 IIIB)

**Epitope** ERDRD

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* poliovirus *Strain:* B clade IIIB *HIV component:* gp41

**Species (Isotype)** mouse

**Ab Type** C-term

**Research Contact** C. Vella or Morag Ferguson (NIBSC, Potters Bar UK)

**References** Holl *et al.* 2006a; Heap *et al.* 2005a; Dimmock 2005; Cleveland *et al.* 2000a; Vella *et al.* 1993; D'Souza *et al.* 1991; Evans *et al.* 1989

**Keywords** dendritic cells, neutralization, review

- 1577: UK Medical Research Council AIDS reagent: ARP317.
- 1577: NIH AIDS Research and Reference Reagent Program: 1172.
- 1577: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 1577: This review summarizes the complex antigenic properties of an external loop in the gp41 tail (Kennedy sequence), highlighting specific MAbs. 1577 and 1583 bind to the epitope ERDRD and do not neutralize virus. Dimmock [2005] (**review**)

- 1577: Unlike SAR1, a MAb that binds near the 1577 epitope within the Kennedy peptide, 1577 cannot inhibit fusion between HIV-1 infected and target cells. Heap *et al.* [2005a]
- 1577: Ab binding to IEEE suppresses neutralizing Ab binding to adjacent epitope ERDRD. Cleveland *et al.* [2000a]
- 1577: Core epitope: ERDRD – could neutralize HIV IIIB and HIV RF. Vella *et al.* [1993]
- 1577: Non-neutralizing in this multi-lab study. D'Souza *et al.* [1991]
- 1577: Raised against IIIB peptide chimera – neutralized African and American HIV-1 lab strains. Evans *et al.* [1989]

No. 782

MAB ID polyclonal (EPES)

HXB2 Location gp160 (739–743)

Author Location gp41 (735–752 IIIB)

Epitope ERDRD

Subtype B

Neutralizing L

Immunogen vaccine

*Vector/Type:* Cowpea mosaic virus *HIV component:* gp41

Species (Isotype) mouse (IgG1, IgG2a, IgG2b)

Ab Type C-term

References Dimmock 2005; McLain *et al.* 2001; Cleveland *et al.* 2000b

Keywords review

- ERDRD-specific IgG recognizes an externalized loop of the gp41 C-terminal domain, and these polyclonal antibodies are the only ones known to bind to this domain that can neutralize cell-free virus. This paper calls these antibodies EPES for Epitope Purified and ERDRD specific. Dimmock [2005] (review)
- The substitution 725 RG (P[R->G]GPDRPEGIEEEGGGERDRDRS) alters the antigenic exposure of this region on the virion resulting in the loss of the downstream neutralizing epitope ERDRD, increased exposure of the epitope GPDRPEG in the virion, while the epitope IEEE remains unchanged. McLain *et al.* [2001]
- ERDRD-specific IgG recognizes an externalized loop of the gp41 C-terminal tail with high affinity – neutralized HIV-1 B clade strains IIIB, NL-4.3, RF, MN and D clade virus CBL-4, but HXB-2D (clade B) was not recognized – when PRGPDRPEGIEEEGGGERDRDRS was used as antigen an immunodominant, non-neutralizing response to IEEE was observed, but immunization GERDRDR shifts the response to ERDRD – NAb does not inhibit attachment of free virus, but does inhibit by an event that precedes fusion-entry. Cleveland *et al.* [2000b]

No. 783

MAB ID DZ

HXB2 Location gp160 (822–855)

Author Location gp41 (827–860 BRU)

Epitope VAEGTDRVIEVVQACRAIRPRIRQGLER-IL

Neutralizing L

Immunogen vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB *HIV component:* EnvSpecies (Isotype) human (IgG1 $\lambda$ )References Boyer *et al.* 1991

- DZ: Weakly neutralizing IIIB – binds to peptides 827-843 and 846-860 of BRU – reacted specifically with IIIB and RF. Boyer *et al.* [1991]

## IV-C-17 Env Antibodies

No. 784

MAB ID

HXB2 Location Env

Author Location gp120 (IIIB)

Epitope

Neutralizing

Immunogen vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* GM-CSF

Species (Isotype) mouse (IgG1)

References Rodríguez *et al.* 1999

- The murine Ab response to a chimeric of granulocyte-macrophage colony stimulating factor GM-CSF/gp120 in vaccinia was not higher titer than the response to a gp120-vaccinia construct, but the breadth of the Ab response was greater, in particular to the C-term region of gp120 – a cellular response of greater intensity was triggered to the GM-CSF/gp120 vaccinia construct, as measured by Elispot assay. Rodríguez *et al.* [1999]

No. 785

MAB ID

HXB2 Location Env

Author Location Env (384–467)

Epitope

Neutralizing

Immunogen vaccine

*Vector/Type:* hepatitis B surface antigen lipoprotein particles (HsBAg) *HIV component:* V3

Species (Isotype) macaque, rabbit

References Michel *et al.* 1993

- Immunization with recombinant HIV1 V3/HBsAg hybrid particles into rabbits or macaques elicited and maintained for several months anti-V3 or HIV-1 Env proliferative, CTL and Ab responses. Michel *et al.* [1993]

No. 786

MAB ID

HXB2 Location Env

Author Location

Epitope

Neutralizing yes

Immunogen HIV-1 infection, vaccine

Species (Isotype) human

References Burton &amp; Parren 2000

- This review article touches on why natural immune responses do not tend to favor potent neutralizing Ab production, and discusses possible vaccine strategies to counter this problem. Burton & Parren [2000]

No. 787  
**MAb ID**  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Pellegrin *et al.* 1996

- Detection of an autologous NAb response in 12 patients with primary infections was delayed – for patients with a viral isolate obtained at month 1, autologous NAb to viral isolates were generally not observed before month 6, and there was no apparent relationship between the emergence of neutralizing activity and the decrease of plasma viral load. Pellegrin *et al.* [1996]

No. 788  
**MAb ID** 1.4C  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human  
**Ab Type** gp120 adjacent to CD4BS  
**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- 1.4C: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 1.4C has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 789  
**MAb ID** 1.4G  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human  
**Ab Type** gp120 adjacent to CD4BS  
**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- 1.4G: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 790  
**MAb ID** 1.9E  
**HXB2 Location** Env  
**Author Location**

**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human  
**Ab Type** gp120 CCR5BS  
**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- 1.9E: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 1.9E has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 791  
**MAb ID** 1.9F  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human  
**Ab Type** gp120 CCR5BS  
**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- 1.9F: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 1.9F has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 792  
**MAb ID** 10/540.w  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** (IgG1)  
**Ab Type** gp120 V3  
**References** Holl *et al.* 2006a

**Keywords** dendritic cells, neutralization

- 10/540.w: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)

No. 793  
**MAb ID** 1010  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** in vitro stimulation or selection  
**Species (Isotype)** human

**Ab Type** gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices  
**Research Contact** G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov

**References** Louis *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation

- 1010: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class B, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 6 +/- 2 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). 1010 and 1018, both class B, were the most potent Fabs. The class B Fabs interact with the six-helix bundle and the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure, antibody generation**)

**No.** 794

**MAb ID** 1014

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** in vitro stimulation or selection

**Species (Isotype)** human

**Ab Type** gp41 six-helix bundle

**Research Contact** G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov

**References** Louis *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation

- 1014: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class A, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 36 +/- 1 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 were about an order of magnitude more potent in this assay than the best Fabs generated here). Class A Fabs interact with the six-helix bundle of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure, antibody generation**)

**No.** 795

**MAb ID** 1018

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** in vitro stimulation or selection

**Species (Isotype)** human

**Ab Type** gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices

**Research Contact** G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov

**References** Louis *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation

- 1018: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class B, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 7 +/- 1 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). 1010 and 1018, both class B, were the most potent Fabs. The class B Fabs interact with the six-helix bundle and the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure, antibody generation**)

**No.** 796

**MAb ID** 1019

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** in vitro stimulation or selection

**Species (Isotype)** human

**Ab Type** gp41 six-helix bundle

**Research Contact** G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov

**References** Louis *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation

- 1019: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class A, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 61 +/- 20 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 were about an order of magnitude more potent in this assay than the best Fabs generated here). Class A Fabs interact with the six-helix bundle of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure, antibody generation**)

**No.** 797

**MAb ID** 102-135

**HXB2 Location** Env

**Author Location** gp41 (HAM112, O group)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* O group  
HAM112 *HIV component:* gp160

**Species (Isotype)** mouse (IgG1κ)

**References** Scheffel *et al.* 1999

- 102-135: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity – 102-135 bound to two non-contiguous peptides in combination, assumed to form some type of helical structure, and not to either individually. Scheffel *et al.* [1999]

**No.** 798  
**MAb ID** 1020  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** in vitro stimulation or selection  
**Species (Isotype)** human  
**Ab Type** gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices  
**Research Contact** G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov  
**References** Louis *et al.* 2005  
**Keywords** antibody binding site definition and exposure, antibody generation

- 1020: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class B, and inhibits LAV mediated Env-mediated cell fusion with an IC<sub>50</sub> of 20 +/- 3 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC<sub>50</sub>s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). The class B Fabs interact with the six-helix bundle and the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure, antibody generation**)

**No.** 799  
**MAb ID** 1022  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** in vitro stimulation or selection  
**Species (Isotype)** human  
**Ab Type** gp41 six-helix bundle and the internal trimeric coiled-coil of N-helices  
**Research Contact** G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov  
**References** Louis *et al.* 2005  
**Keywords** antibody binding site definition and exposure, antibody generation

- 1022: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class B, and inhibits LAV mediated Env-mediated cell fusion with an IC<sub>50</sub> of 40 +/- 10 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC<sub>50</sub>s of 0.5-1.5 ug/ml) were about an order of

magnitude more potent in this assay than the best Fabs generated here). The class B Fabs interact with the six-helix bundle and the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure, antibody generation**)

**No.** 800  
**MAb ID** 1025  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**  
**References** Berman *et al.* 1997

- 1025: Binds to 1/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997]

**No.** 801  
**MAb ID** 1034  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Subtype** B  
**Neutralizing**

**Immunogen** in vitro stimulation or selection  
**Species (Isotype)** human

**Ab Type** gp41 internal trimeric coiled-coil of N-helices  
**Research Contact** G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov  
**References** Louis *et al.* 2005  
**Keywords** antibody binding site definition and exposure, antibody generation

- 1034: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class C, and inhibits LAV mediated Env-mediated cell fusion with an IC<sub>50</sub> of 17 +/- 2 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC<sub>50</sub>s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). The class C Fabs interact with the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure, antibody generation**)

**No.** 802  
**MAb ID** 105-134  
**HXB2 Location** Env  
**Author Location** gp41 (652–681 HAM112, O group)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* O group HAM112 *HIV component:* gp160

**Species (Isotype)** mouse (IgG1κ)

**References** Scheffel *et al.* 1999

- 105-134: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity. Scheffel *et al.* [1999]

No. 803  
**MAB ID** 10E9  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** mouse (IgG1)  
**References** Papsidero *et al.* 1988  
 • 10E9: 100/100 HIV+ human sera could inhibit 10E9 binding. Papsidero *et al.* [1988]

No. 804  
**MAB ID** 12.19  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** (IgG)  
**Ab Type** gp120 V3  
**References** Koefoed *et al.* 2005  
**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics  
 • 12.19: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. This antibody bound to a V3-fusion protein. Koefoed *et al.* [2005] (antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain)

No. 805  
**MAB ID** 12.9  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** (IgG)  
**Ab Type** gp120 V3  
**References** Koefoed *et al.* 2005  
**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics  
 • 12.9: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. This antibody bound to a V3-fusion protein. Koefoed *et al.*

[2005] (antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain)

No. 806  
**MAB ID** 126-50  
**HXB2 Location** Env  
**Author Location** gp41 (HXB2)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG2κ)  
**References** Xu *et al.* 1991; Robinson *et al.* 1991; Tyler *et al.* 1990; Robinson *et al.* 1990b  
 • 126-50: No enhancing or neutralizing activity. Robinson *et al.* [1991]  
 • 126-50: Specific for a conformational epitope. Xu *et al.* [1991]  
 • 126-50: No enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b]  
 • 126-50: Serves as target for antibody-dependent cellular cytotoxicity ADCC. Tyler *et al.* [1990]

No. 807  
**MAB ID** 12H2  
**HXB2 Location** Env  
**Author Location** gp41 (530–677 HXB2)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* Semliki-Forest Virus *HIV component:* Env  
**Species (Isotype)** mouse (IgMκ)  
**References** Giraud *et al.* 1999  
 • 12H2: Env in a Semliki-Forest Virus (SFV) vector was used to vaccinate mice intramuscularly as naked RNA, and an Ab response was induced to Env from which 12H2 was derived – and advantage of this method is that the protein is properly expressed. Giraud *et al.* [1999]

No. 808  
**MAB ID** 13.10 (No. 13)  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1λ)  
**Research Contact** Evan Hersh and Yoh-Ichi Matsumoto  
**References** Wisniewski *et al.* 1996; Moran *et al.* 1993; Lake *et al.* 1989  
 • 13.10: NIH AIDS Research and Reference Reagent Program: 377.  
 • 13.10: 13.10 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996]

- 13.10: Heavy (V HI) and light (V lambdaII) chain sequenced – no enhancing or neutralizing activity – called No. 13. Moran *et al.* [1993]
- 13.10: First HIV-1 specific human-mouse hybridoma that produces a MAbs that binds to gp120 and gp160. Lake *et al.* [1989]

No. 809

**MAB ID** 1331-D

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)**

**References** Eda *et al.* 2006b

**Keywords** variant cross-recognition or cross-neutralization

- 1331-D: The neutralization potency of this Ab against 7 HIV-1 primary isolates was compared to the neutralization potency of the Ab KD-247. Higher concentrations of 1331-D were needed for the neutralization of all of the HIV-1 isolates suggesting a lower neutralization potency of this Ab. Eda *et al.* [2006b] (**variant cross-recognition or cross-neutralization**)

No. 810

**MAB ID** 13H11

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Subtype** M

**Neutralizing** No

**Immunogen** vaccine

*Strain:* M group Consensus *HIV component:* gp140

**Species (Isotype)** mouse

**Ab Type** gp41 adjacent to cluster II, gp41 MPER (membrane proximal external region)

**Research Contact** Barton Haynes, Duke University, Durham, NC, USA, haynes002@mc.duke.edu

**References** Alam *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody interactions

- 13H11: This was a non-neutralizing anti-gp41 membrane proximal antibody raised in mice immunized with an M group consensus (Con-S) HIV-1 gp140 oligomer that expressed the 2F5 epitope. Like 2F5, 13H11 bound to the gp140 heptad repeat-2 peptide (DP178) and could cross-block binding of 2F5 to DP178. Unlike 2F5, 13H11 could not bind to phospholipids, including cardiolipin, and cannot neutralize primary isolates. Alam *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, antibody interactions**)

No. 811

**MAB ID** 13a15

**HXB2 Location** Env

**Author Location** (JRFL)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4BS

**References** Koefoed *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13a15: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13a15 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain**)

No. 812

**MAB ID** 13a23

**HXB2 Location** Env

**Author Location** (JRFL)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4BS

**References** Koefoed *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13a23: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs; 13a23 was somewhat different from the other CD4BS Fabs isolated in this study, in that its binding was enhanced by anti-C1 MAbs. Fab 13a23 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain**)

No. 813

**MAB ID** 13a3

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)



**Ab Type** gp120 CD4BS

**References** Koefoed *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13a3: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13a3 weakly neutralized MN, but not HXB2 Ba-L or JRFL. Koefoed *et al.* [2005] (**antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain**)

**No.** 814

**MAb ID** 13a6

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4BS

**References** Koefoed *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13a6: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to using bone marrow for generating libraries, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13a6 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain**)

**No.** 815

**MAb ID** 13a7

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4BS

**References** Koefoed *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13a7: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13a7 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain**)

**No.** 816

**MAb ID** 13b53

**HXB2 Location** Env

**Author Location** (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4BS

**References** Koefoed *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13b53: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13b53 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain**)

**No.** 817

**MAb ID** 13b61

**HXB2 Location** Env

**Author Location** (LAI)

**Epitope**

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4BS

**References** Koefoed *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13b61: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected

library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13b61 could neutralize HXB2 at 25 ug/ml, but not MN, Ba-L or JRFL. Koefoed *et al.* [2005] (**antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain**)

**No.** 818

**Mab ID** 1492

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** in vitro stimulation or selection

**Species (Isotype)** human

**Ab Type** gp41 internal trimeric coiled-coil of N-helices

**Research Contact** G. Marius Clore or Carole Bewley, NIH, Bethesda, Maryland. marius@intra.niddk.nih.gov or caroleb@mail.nih.gov

**References** Louis *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation

- 1492: This is one of nine anti-gp41 bivalent Fabs selected from a non-immune human phage display library. This Fab was classified as class C, and inhibits LAV mediated Env-mediated cell fusion with an IC50 of 25 +/- 2 ug/ml (the range for the 9 new Fabs was 6-61 ug/ml – for context, 2F5 and 2G12 (IC50s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here). The class C Fabs interact with the internal coiled-coil of N-helices of gp41. Louis *et al.* [2005] (**antibody binding site definition and exposure, antibody generation**)

**No.** 819

**Mab ID** 1B1

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Research Contact** Herman Katinger, Inst. Appl. Microbiol. University of Agricultural Science, Vienna, Austria

**References** Kunert *et al.* 1998; Purtscher *et al.* 1994; Buchacher *et al.* 1994

- 1B1: The complete V, J and D(H) domain was sequenced – unlike non-neutralizing anti-gp41 Mab 3D6, five neutralizing MAbs (2F5, 2G12, 1B1, 1F7, and 3D5) showed extensive somatic mutations giving evidence of persistent antigenic pressure over long periods. Kunert *et al.* [1998]
- 1B1: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994]

**No.** 820

**Mab ID** 1D10

**HXB2 Location** Env

**Author Location** gp120 (34–55)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

**Species (Isotype)**

**Research Contact** Phil Berman

**References** Callahan *et al.* 1991

- 1D10: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interactions mediated through the local high positive charge density in the V3 loop. The binding of this N-term binding antibody is increased by dextran sulfate, in contrast to anti-V3 antibodies that are inhibited. Callahan *et al.* [1991]

**No.** 821

**Mab ID** 1F7

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Research Contact** Herman Katinger, Inst. Appl. Microbiol. University of Agricultural Science, Vienna, Austria

**References** Grant *et al.* 2000; Kunert *et al.* 1998; Purtscher *et al.* 1994; Buchacher *et al.* 1994

- 1F7: There is an anti-idiotypic Mab named 1F7 that was raised against pooled IgG from HIV-1 + subjects that recognizes a set of antibodies against HIV Gag, Pol, and Env, and this Mab is reported to inhibit anti-HIV CTL activity—this is not the same as the 1F7 described by Buchacher *et al.*. Grant *et al.* [2000]
- 1F7: The complete V, J and D(H) domain was sequenced – unlike non-neutralizing anti-gp41 Mab 3D6, five neutralizing MAbs (2F5, 2G12, 1B1, 1F7, and 3D5) showed extensive somatic mutations giving evidence of persistent antigenic pressure over long periods. Kunert *et al.* [1998]
- 1F7: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994]

**No.** 822

**Mab ID** 2.5E

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CCR5BS

**References** Haynes *et al.* 2005

- Keywords** antibody binding site definition and exposure
- 2.5E: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such

autoreactivity. 2.5E has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 823  
**MAb ID** 25G  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human  
**Ab Type** gp120 CD4BS  
**References** Haynes *et al.* 2005  
**Keywords** antibody binding site definition and exposure

- 25G: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 25G has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 824  
**MAb ID** 2601  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** A, CRF02\_AG  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 V3  
**References** Krachmarov *et al.* 2005  
**Keywords** antibody binding site definition and exposure, subtype comparisons, variant cross-recognition or cross-neutralization

- 2601: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. 2601 was derived from a person infected with a clade A or CRF02 virus, and binds to A but not to B V3 loops. Neutralization of JR-FL and SF162(UG V3) by anti-V3 MAbs 2557, 2558, 2601, but not subtype A primary isolates despite binding to the subtype A V3 loops, suggested masking by V1V2 blocking of neutralization by these antibodies. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 825  
**MAb ID** 2909  
**HXB2 Location** Env  
**Author Location**  
**Epitope**

**Subtype B**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**Ab Type** quaternary structure  
**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu), NYU, NY  
**References** Honnen *et al.* 2007; Gorny *et al.* 2005  
**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, subtype comparisons, variant cross-recognition or cross-neutralization

- 2909: Replacing V3 domain of SF162, which is neutralized by 2909, with V3 from different HIV-1 clades resulted in significant reductions in sensitivity to neutralization by this antibody. However, the only variant totally resistant was CRF01\_AE. The main requirement for reactivity of 2909 in V2 was a rare polymorphism at position 160 or 161, and to a lesser extent at positions 167 and 169. It was also found that the neutralization sensitive SF162 variant actually expressed a suboptimal form of 2909 epitope where a mutation N167D resulted in more robust neutralization. Position 167 in V2 dictates the specificities of three type-specific neutralizing MAbs that bind to an otherwise relatively conserved epitope in involving V2: 2909, C108g, and 10/76b. Honnen *et al.* [2007] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 2909: 2909 is a NAb that was produced by fusion of heteromyeloma SHM-D33 with Epstein-Barr virus transformed PBMC and selection by a neutralization assay. The PBMC were derived from an HIV-1 infected individual who maintained a low viral load after 15 years of infection with no therapy. The MAb very potently neutralizes SF162, but has a narrow range of activity, and did not neutralize autologous virus, nor primary isolates from clade A (VI191, CA1, and 92RW021), clades B (BX08, CA5, and BaL), clade C (95ZW2036) and clade F (CA20 and 93BR029). Sequence analysis of the variable domain of the heavy chain of 2909 shows that it is comprised of IgHV3-43, IgHJ6, and IgHD5-12. 2909 reorganizes a quaternary structure present on intact SF162 virions and does not bind to soluble or recombinant Envelope proteins. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670 (anti-C5), 1418 (irrelevant control MAb), nor 2G12 (anti-carbohydrate); in fact, 2G12 enhanced 2909 binding. Gorny *et al.* [2005] (**antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons, antibody sequence variable domain**)

No. 826  
**MAb ID** 2G12 (c2G12)  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Subtype B**  
**Neutralizing** L P  
**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 carbohydrates at glycosylation residues in C2, C3, C4, and V4

**Research Contact** Herman Katinger, Inst. Appl. Microbiol. or Polymun Scientific Inc., Vienna, Austria,

**References** Gray *et al.* 2006; Joos *et al.* 2006; Braibant *et al.* 2006; Davis *et al.* 2006; Cham *et al.* 2006; Holl *et al.* 2006a; Herrera *et al.* 2006; Law *et al.* 2007; Huskens *et al.* 2007; Huang *et al.* 2007a; Honnen *et al.* 2007; Haim *et al.* 2007; Dey *et al.* 2007; Kothe *et al.* 2007; Ferrantelli *et al.* 2007; Dhillon *et al.* 2007; Bowley *et al.* 2007; Blish *et al.* 2007; Billington *et al.* 2007; Liao *et al.* 2006; Holl *et al.* 2006b; Haynes & Montefiori 2006; Selvarajah *et al.* 2005; Raviv *et al.* 2005; Pinter *et al.* 2005; Pashov *et al.* 2005; Nakowitsch *et al.* 2005; Martín-García *et al.* 2005; Lusso *et al.* 2005; Louis *et al.* 2005; Krachmarov *et al.* 2005; Haynes *et al.* 2005; Gorny *et al.* 2005; Chen *et al.* 2005; Calarese *et al.* 2005; Wang *et al.* 2004; Safrit *et al.* 2004; Pugach *et al.* 2004; Pinter *et al.* 2004; Pantophlet *et al.* 2004; Opalka *et al.* 2004; Nabatov *et al.* 2004; Lorin *et al.* 2004; Liao *et al.* 2004; Jeffs *et al.* 2004; Ferrantelli *et al.* 2004a; Ferrantelli *et al.* 2004b; Dacheux *et al.* 2004; Biorn *et al.* 2004; Binley *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Wolbank *et al.* 2003; Ohagen *et al.* 2003; Montefiori *et al.* 2003; Louis *et al.* 2003; Kitabwalla *et al.* 2003; Raja *et al.* 2003; Singh *et al.* 2003; Wang 2003; Richman *et al.* 2003; Mascola 2003; Mascola *et al.* 2003; Hart *et al.* 2003; Ferrantelli *et al.* 2003; Dey *et al.* 2003; Cavacini *et al.* 2003; Binley *et al.* 2003; Abrahamyan *et al.* 2003; Albu *et al.* 2003; Herrera *et al.* 2003; Pantophlet *et al.* 2003a; Choe *et al.* 2003; Calarese *et al.* 2003; Stiegler *et al.* 2002; Kwong *et al.* 2002; Gorry *et al.* 2002; Cavacini *et al.* 2002; Bures *et al.* 2002; Liu *et al.* 2002; Ferrantelli & Ruprecht 2002; Zhang *et al.* 2002; Mascola 2002; Grundner *et al.* 2002; Edwards *et al.* 2002; Armbruster *et al.* 2002; Chakrabarti *et al.* 2002; Xu *et al.* 2002; Yang *et al.* 2002; Schulke *et al.* 2002; Scanlan *et al.* 2002; Sanders *et al.* 2002; Golding *et al.* 2002b; Savarino *et al.* 2001; Xu *et al.* 2001; Hofmann-Lehmann *et al.* 2001; Spenlehauer *et al.* 2001; Stiegler *et al.* 2001; Verrier *et al.* 2001; Zeder-Lutz *et al.* 2001; Poignard *et al.* 2001; Moore *et al.* 2001; Barnett *et al.* 2001; Zwick *et al.* 2001c; Mascola & Nabel 2001; Si *et al.* 2001; Park *et al.* 2000; Grovit-Ferbas *et al.* 2000; Baba *et al.* 2000; Robert-Guroff 2000; Binley *et al.* 1999; Mascola *et al.* 2000; Mascola *et al.* 1999; Parren *et al.*

1999; Poignard *et al.* 1999; Crawford *et al.* 1999; Altmeyer *et al.* 1999; Beddows *et al.* 1999; Montefiori & Evans 1999; Schonning *et al.* 1998; Kunert *et al.* 1998; Frankel *et al.* 1998; Wyatt & Sodroski 1998; Li *et al.* 1998; Parren *et al.* 1998b; Takefman *et al.* 1998; Fouts *et al.* 1998; Trkola *et al.* 1998; Binley *et al.* 1998; Connor *et al.* 1998; Sullivan *et al.* 1998b; Parren *et al.* 1998a; Mondor *et al.* 1998; Wyatt *et al.* 1998; Andrus *et al.* 1998; Parren *et al.* 1997b; Burton & Montefiori 1997; Ugolini *et al.* 1997; Mascola *et al.* 1997; Moore & Trkola 1997; Li *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Mo *et al.* 1997; D'Souza *et al.* 1997; Sattentau 1996; Trkola *et al.* 1996a; Poignard *et al.* 1996b; Moore & Sodroski 1996; Trkola *et al.* 1996b; McKeating 1996; McKeating *et al.* 1996; Moore & Ho 1995; Trkola *et al.* 1995; Buchacher *et al.* 1994

**Keywords** acute/early infection, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, autologous responses, binding affinity, brain/CSF, co-receptor, complement, dendritic cells, enhancing activity, escape, immunoprophylaxis, immunotherapy, isotype switch, kinetics, mother-to-infant transmission, mucosal immunity, neutralization, responses in children, review, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization, viral fitness and reversion

- 2G12: UK Medical Research council AIDS reagent: ARP3030.
- 2G12: NIH AIDS Research and Reference Reagent Program: 1476.
- 2G12: This Ab was found to be able to bind to a highly stable trimeric rgp140 derived from a HIV-1 subtype D isolate containing intermonomer V3-derived disulfide bonds and lacking gp120/gp41 cleavage. Billington *et al.* [2007]
- 2G12: 15 subtype A HIV-1 envelopes from early in infection were not neutralized by 2G12, likely because of a deletion or shift in one or more of the 5 glycosylation sites associated with 2G12 recognition. SF162 was neutralized as expected. Blish *et al.* [2007] (**neutralization, acute/early infection, subtype comparisons**)
- 2G12: Yeast display was compared to phage display and shown to select all the scFv identified by phage display and additional novel antibodies. Biotinylated C11 and 2G12 were used to minimize selection of non-gp120 specific clones from the yeast displayed antibody library; these MABs were used as they have unique epitopes with limited overlap with most known epitopes. Bowley *et al.* [2007] (**assay standardization/improvement**)

- 2G12: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP trimers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. Dey *et al.* [2007]
- 2G12: This Ab was used to help define the antigenic profile of envelopes used in serum depletion experiments to attempt to define the neutralizing specificities of broadly cross-reactive neutralizing serum. It bound to JR-FL and JR-CSF gp120 monomers and to a lesser extent to core JR-CSF gp120 monomer. Dhillon *et al.* [2007] (**antibody binding site definition and exposure, neutralization**)
- 2G12: Newborn macaques were challenged orally with the highly pathogenic SHIV89.6P and then treated intravenously with a combination of IgG1b12, 2G12, 2F5 and 4E10 one and 12 hours post-virus exposure. All control animals became highly viremic and developed AIDS. In the group treated with mAbs 1 hour post-virus exposure, 3/4 animals were protected from persistent systemic infection and one was protected from disease. In the group treated with mAbs 12 hour post-virus exposure, one animal was protected from persistent systemic infection and disease was prevented or delayed in two animals. IgG1b12, 2G12, and 4E10 were also given 24 hours after exposure in a separate study; 4/4 treated animals become viremic, but with delayed and lower peak viremia relative to controls. 3/4 treated animals did not get AIDS during the follow up period, and 1 showed a delayed progression to AIDS, while the 4 untreated animals died of AIDS. Thus the success of passive immunization with NAb depends on the time window between virus exposure and the start of immunoprophylaxis. Ferrantelli *et al.* [2007] (**immunoprophylaxis**)
- 2G12: Controlled attachment of Ab-bound HIV to cells was not affected by the presence of this Ab. However, the virus was still efficiently neutralized indicating that binding of 2G12 to the cell-free virus interferes with a step of infection subsequent to cell attachment. Haim *et al.* [2007] (**neutralization, variant cross-recognition or cross-neutralization, kinetics**)
- 2G12: The neutralizing activity of this antibody for the JR-FL Env variant with the N160K/E160K mutations was measured in comparison with the neutralizing activity of 2909, which was found to be higher. Honnen *et al.* [2007] (**neutralization**)
- 2G12: Binding of 2G12 to gp120 was not significantly affected by the small molecule HIV-1 entry inhibitor IC9564. IC9564 induces conformational change of gp120 to allow CD4i antibody 17b to bind, but inhibits CD4-induced gp41 conformational changes. Huang *et al.* [2007a]
- 2G12: Cross-neutralization was limited in this study. 2G12 neutralized subtype A strain UG273 and subtype B strains US2, NL4-3, and IIB. It did not neutralize subtype C strain ETH2220, subtype D UG270, CRF01 A/E ID12; subtype F BZ163; nor subtype G BCF06. 3 HIV-2 strains and SIVmac 251 were also not neutralized. 2G12 bound to MN and NDK, but did not neutralize them. Neutralization resistance was selected in culture using strains NL43 and IIB. NL43 escaped via loss of the glycosylation sequon at positions 295-297, IIB escaped via sequon losses at positions 392-394 and 295-297, or 406-408, as expected from earlier studies defining critical mannose residues for 2G12 binding. The loss of the mannose actually enhanced mannose-specific lectin inhibition of the virus. Huskens *et al.* [2007] (**antibody binding site definition and exposure, neutralization, variant cross-recognition or cross-neutralization, escape**)
- 2G12: Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 co-receptor. Primary isolate Envs were completely resistant or just somewhat sensitive to neutralization by 2G12 while the consensus B constructs were sensitive. Thus the 2G12 epitope is present on the consensus B Env glycoprotein and was not influenced by the Env modifications in this study. Kothe *et al.* [2007] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)
- 2G12: G1 and G2 recombinant gp120 proteins, consisting of 2F5 and 4E10, and 4E10 epitopes, respectively, engrafted into the V1/V2 region of gp120, were tested as an immunogen to see if they could elicit MPER antibody responses. Deletion of V1/V2 from gp120 or its replacement with G1 and G2 grafts, did not greatly affect binding of 2G12 to gp120. Shortening of the N and C termini of the V3 loop nearly abolished binding of 2G12. Law *et al.* [2007] (**vaccine antigen design**)
- 2G12: Inhibition of 2G12 binding to gp120 by 2G12-like Abs in sera from long-term non-progressors (LTNP) was determined. 2G12-like Abs were present in almost all sera from LTNPs but at a lower levels than b12. Higher 2G12-like Ab levels were significantly associated with the broadest neutralizing activity in sera from LTNPs. Braibant *et al.* [2006] (**enhancing activity, neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 2G12: Cloned Envs (clades A, B, C, D, F1, CRF01\_AE, CRF02\_AG, CRF06\_cpx and CRF11\_cpx) derived from donors either with or without broadly cross-reactive neutralizing antibodies were shown to be of comparable susceptibility to neutralization by 2G12. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 2G12: Neutralization rates and rate constants for the neutralization of clade B primary isolates SF33, SF162 and 89.6 by this Ab were determined. Statistically significant neutralization was not observed for isolate SF162. It was shown that neutralization sensitivity is not associated with neutralization of cell-associated or free virus. Davis *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, kinetics**)
- 2G12: Env-pseudotyped viruses were constructed from the gp160 envelope genes from seven children infected with subtype C HIV-1. 2G12 failed to neutralize any of the seven viruses, correlating with the absence of crucial N-linked glycans that define 2G12 epitope on these viruses. When

this Ab was mixed with IgG1b12 and 2F5, the neutralization was similar as to IgG1b12 alone, indicating that the majority of the pool activity was due to IgG1b12. When 4E10 was added to this mix, all isolates were neutralized. Gray *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, responses in children, mother-to-infant transmission**)

- 2G12: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure, neutralization, variant cross-recognition or cross-neutralization, escape**)
- 2G12: Viruses with cleavage-competent 2G12-knockout Env and cleavage-defective Env able to bind 2G12 were constructed. The amount of Env precipitated by 2G12 was same when the two pseudotyped virus variants were mixed as with the wildtype alone, suggesting formation of heterotrimers consisting of both cleavage-competent and defective Envs. The presence of nonfunctional Envs on the surface of infectious virions did not affect the neutralization by 2G12. The neutralization by the CD4-binding agents was also unaffected by 2G12 binding to uncleaved Env indicating that the function of a trimer is unaffected sterically by the binding of an antibody to adjacent trimer. Herrera *et al.* [2006] (**neutralization, binding affinity**)
- 2G12: Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in iMDDCs was evaluated. The neutralizing activity of 2G12 was higher in iMDDCs than in PHA-stimulated PBMCs. A 90% reduction of HIV infection was observed without induction of MDDC maturation by this mAb. Blockade of FcγRII on iMDDCs decreased the anti-HIV activity of 2G12 while increased expression of FcγRI increased inhibition of HIV by 2G12, suggesting the involvement of these receptors in the HIV-inhibitory activity of this Ab. Holl *et al.* [2006b] (**neutralization, dendritic cells**)
- 2G12: The ability of this Ab to inhibit viral growth was increased when macrophages and immature dendritic cells (iDCs) were used as target cells instead of PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 2G12: Pharmacokinetic properties of this Ab were studied in HIV infected patients infused with high doses of 2G12. The Ab did not elicit an endogenous immune response and had distribution and systemic clearance values similar to other Abs. The elimination half-life was measured to 21.8 days, which is significantly longer than the elimination half-life of 4E10 and 2F5. Joos *et al.* [2006] (**kinetics, immunotherapy**)
- 2G12: The gp140 $\delta$ CFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. 2G12 was shown to bind specifically to all recombinant proteins except for the subtype B gp140 $\delta$ CF and subtype A gp140 $\delta$ CFI. The specific binding of this Ab to CON-S indicated that its conformational epitope was intact. This Ab also bound specifically to the two tested subtype B gp120 proteins. Liao *et al.* [2006] (**antibody binding site definition and exposure, vaccine antigen design, subtype comparisons**)
- 2G12: Precise characterization of 2G12 binding to carbohydrate was undertaken; the 2G12 Fab was co-crystallized with four oligomannose derivatives, Man4, Man5, Man7 and Man8. 2G12 recognizes the terminal Man $\alpha$ 1-2Man both in the context of the D1 arm (Man $\alpha$ 1-2Man $\alpha$ 1-2Man) and D3 arm (Man $\alpha$ 1-2Man $\alpha$ 1-6Man) of the Man9GlcNAc2 moiety, but not the D2 arm. This gives the 2G12 more binding flexibility than previously thought, as only the D1 arm binding had been shown previously. Calarese *et al.* [2005] (**antibody binding site definition and exposure, structure**)
- 2G12: The lack of glycosylation sites at residues Asn 295 and Thy 394 within C-clade gp120s generally causes the loss of 2G12 recognition. Introduction of glycans in the subtype C strain HIV-1CN54 at these positions restored 2G12 binding, and addition of just a single glycan partially restored binding (V295N + A394T  $\gg$  V295N  $>$  A395T). 2G12 epitope recovery decreased b12 binding. Chen *et al.* [2005] (**antibody binding site definition and exposure**)
- 2G12: 2909 is a human anti-Env NAb that was selected by a neutralization assay and binds to the quaternary structure on the intact virion. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670, 1418, nor 2G12; in fact, 2G12 enhanced 2909 binding. Gorny *et al.* [2005]
- 2G12: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. Unlike the other three broadly neutralizing human anti-HIV-1 MAbs, 2G12 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)
- 2G12: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Neutralization by Cameroonian sera MAbs was blocked by Clade A and B V3 loop fusion proteins, while NAb to non-V3 epitopes, 2F5, 2G12, and b12, were not blocked. Krachmarov *et al.* [2005] (**antibody bind-**

- ing site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons)**
- 2G12: Nine anti-gp41 bivalent Fabs that interacted with either or both of the six-helix bundle and the internal coiled-coil of N-helices of gp41 were selected from a non-immune human phage display library. The IC<sub>50</sub> the range for the inhibition of LAV ENV-mediated cell-fusion was 6-61 ug/ml – for context, 2F5 and 2G12 (IC<sub>50</sub>s of 0.5-1.5 ug/ml) were about an order of magnitude more potent in this assay than the best Fabs generated here. Louis *et al.* [2005] (**neutralization**)
  - 2G12: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication in microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using CD4BS MAbs F105 and IgG1b12, glycan-specific 2G12, and V3-specific 447-52D, and were unchanged. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Martín-García *et al.* [2005] (**antibody binding site definition and exposure**)
  - 2G12: Passive immunization of 8 HIV-1 infected patients with 4E10, 2F5 and 2G12 (day 0, 4E10; days 7, 14 and 21 4E10+2G12+2F5; virus isolated on days 0 and 77) resulted in 0/8 patients with virus that escaped all three NABs. Three patients had viruses that escaped 2G12, and two of these were sequenced. Each had lost two of the glycosylation sites required for 2G12 binding (one had 295 N->D and 332 N->T changes, the other had 295 N->T and 392 N->T changes). In a companion in vitro study, resistance to a single MAb emerged in 3-22 weeks, but triple combination resistance was slower and characterized by decreased viral fitness. In contrast to the in vivo escape study, only one N was lost in the in vitro experiments, a 386 N->K change in a triple resistant mutant. The lack of resistance to the combination of MAbs in vivo and the reduced fitness of the escape mutants selected in vitro suggests passive immunotherapy may be of value in HIV infection. Nakowitsch *et al.* [2005] (**escape, immunotherapy**)
  - 2G12: Concanavalin A (ConA) binds to mannose and blocks 2G12 binding, but 2G12 does not block ConA binding. ConA binding is less sensitive to mutations in glycosylation sites than 2G12. Furthermore, ConA neutralizes HIV-1 at a post-CD4 binding step. Thus, this report indicates that designing antigens based on the HIV-1 mannose residues that bind ConA may be an effective vaccine strategy, as antibodies elicited might be broadly cross-reactive. Pashov *et al.* [2005] (**vaccine antigen design**)
  - 2G12: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potentially neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MAbs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
  - 2G12: Retrovirus inactivation for vaccine antigen delivery was explored through lipid modification by hydrophobic photoinduced alkylating probe 1.5 iodonaphthylazide (INA). The viral proteins were shown to be structurally intact in the treated non-infectious virus, through the preservation of antibody binding sites for polyclonal anti-gp120 serum, and for broadly neutralizing MAbs 2G12, b12 and 4E10, although the modifications of the lipid disabled viral infection. Raviv *et al.* [2005] (**vaccine antigen design**)
  - 2G12: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. 2G12 had diminished binding to both antigen constructs. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
  - 2G12: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. 2G12 primarily neutralized B clade viruses with sporadic neutralization of A, D, and two AC recombinants, and no C or CRF01 (E) isolates. Envelopes from subtypes C and E have generally lost critical glycans for 2G12 binding. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 2G12: The peptide 12p1 (RINNIPWSEAMM) inhibits direct binding of YU2 gp120 or Env trimer to CD4, CCR5 and MAb 17b in a concentration-dependent allosteric manner. 12p1 is thought to bind to unbound gp120 near the CD4 binding site, with a 1:1 stoichiometry. 12p1 also inhibited MAb F105 binding. presumably because F105 favors an unactivated conformation, but not MAbs 2G12 or b12. The 1:1 stoichiometry, the fact that the peptide binding site is accessible on the trimer, the non-CD4 like aspect of the binding, and an ability to inhibit viral infection in cell cultures make it a promising lead for therapeutic design. Biorn *et al.* [2004]
  - 2G12: Env sequences were derived from 4 men at primary infection and four years later; the antigenicity in terms of the ability to bind to 2G12, 2F5 and IgG1b12 was determined. 2G12 bound primarily to late clones in 3 of the 4 patients, and to both early and late in the other patient. Neither 2F5 nor IgG1b12 showed a difference in binding affinity to early or late envelopes. The number of glycosylation sites increased in the three patients. The ability to bind to 2G12 correlated perfectly with having all three sites known to be important for binding: N295 in C2, N332 in C3, and N392 in the V4 loop. Dacheux *et al.* [2004] (**antibody binding site definition and exposure, acute/early infection, kinetics**)
  - 2G12: Neonatal rhesus macaques were exposed orally to a pathogenic SHIV, 89.6P. 4/8 were given an intramuscular, passive immunization consisting of NABs 2G12, 2F5 and 4E10, each given at a different body sites at 40 mg/kg per Ab, at one hour and again at 8 days after exposure to 89.6P. The four animals that were untreated all died with a mean survival time

- of 5.5 weeks, the four animals that got the NAb combination were protected from infection. This model suggests Abs may be protective against mother-to-infant transmission of HIV. Ferrantelli *et al.* [2004b] (**mother-to-infant transmission**)
- 2G12: Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. 2G12 didn't neutralize O group strains, although it was included in a quadruple combination of b12, 2F5, 2G12, and 4E10, that neutralized the six Group O viruses between 62-97%. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)
  - 2G12: This paper is a review of anti-HIV-1 Envelope antibodies. This unique epitope is formed from carbohydrates. The mechanism of MAb neutralization is thought to be steric inhibition of CCR5 binding. 2G12 neutralizes many TCLA strains and about 40% of primary isolates tested. Gorny & Zolla-Pazner [2004] (**review**)
  - 2G12: A set of oligomeric envelope proteins were made from six primary isolates for potential use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. 2G12 bound to clade A, B, D and F HIV-1 primary isolates. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design, subtype comparisons**)
  - 2G12: 2G12 was used as a positive control in a study that showed that A32-rgp120 complexes open up the CCR5 co-receptor binding site, but did not induce neutralizing antibodies with greater breadth among B subtype isolates than did uncomplexed rgp120 in vaccinated guinea pigs. Liao *et al.* [2004] (**vaccine antigen design**)
  - 2G12: Mice susceptible to MV infection were intraperitoneally immunized with native HIV-1 89.6 env gp160 and gp140 and  $\delta$ V3 HIV-1 89.6 mutants expressed in live attenuated Schwarz measles vector (MV). The gp160 $\Delta$ V3 construct raised more cross-reactive NAbs to primary isolates. A HIVIG/2F5/2G12 combination was used as a positive control and could neutralize all isolates. Lorin *et al.* [2004] (**vaccine antigen design**)
  - 2G12: A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4 viruses were more sCD4 and 2G12 neutralization resistant than either R5 or X4, but the opposite pattern was observed for b12. Addition of the late stage V1V2 altered neutralization for both MAbs, but this alteration was reversed with the loss of the V3 glycan. Nabatov *et al.* [2004] (**antibody binding site definition and exposure, co-receptor**)
  - 2G12: An antigen panel representing different regions of gp41 was generated, and sera from 23 individuals were screened. 2G12 was a control, binding to gp120 but to none of the gp41 peptides in the experiment. Opalka *et al.* [2004] (**assay development, assay standardization/improvement**)
  - 2G12: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it binds to the neutralizing MAb 2G12. It masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120. Pantophlet *et al.* [2004] (**vaccine antigen design**)
  - 2G12: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 2G12 was the only MAb that neutralized JRFL more efficiently than SF162, with a 6-fold lower ND50 for JRFL. 2G12 also had a higher affinity for JRFL. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
  - 2G12: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAB b12 and sCD4 that was attributed to changes in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CC-con19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. The IC50 for 2G12 was 1.8 for CC1/85, and was 4.2 for CC-con19, so both the primary and passaged viruses were neutralized. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization, viral fitness and reversion**)
  - 2G12: This review discusses research presented at the Ghent Workshop of prevention of breast milk transmission and immunoprophylaxis for HIV-1 in pediatrics (Seattle, Oct. 2002), and makes the case for developing passive or active immunoprophylaxis in neonates to prevent mother-to-infant transmission. Macaque studies have shown that passive transfer of NAb combinations (for example, IgG1b12, 2G12, 2F5, and 4E10; or 2G12 and 2F5) can confer partial or complete protection to infant macaques from subsequent oral SHIV challenge. Safrit *et al.* [2004] (**immunoprophylaxis, mother-to-infant transmission**)
  - 2G12: Synthetic mannose Man9 clusters arranged on a scaffold were used to mimic the epitope of 2G12. Bi-, tri-, and tetra-valent clusters had a 7-, 22-, and 73-fold higher affinities for 2G12 than the monomers, suggesting that 2G12 binds best to multiple carbohydrate moieties. 2G12 bound larger mannose oligosaccharides with higher affinity: Ma9GlcNAc



- bound 210- and 74-fold more effectively than Man6GlcNac and Man5GlcNac, respectively. Wang *et al.* [2004] (**antibody binding site definition and exposure**)
- 2G12: SOS-Env is a mutant protein engineered to have a disulfide bond between gp120 and gp41. Cells expressing SOS-Env do not fuse with target cells expressing CD4 and CCR5, although the fusion process proceeds to an intermediate state associated with CD4 and co-receptors, prior to the formation of the six helix bundle that allows fusion. 2G12 was used to monitor surface expression of SOS-Env compared to wildtype. Abrahamyan *et al.* [2003] (**co-receptor, vaccine antigen design**)
  - 2G12: 2G12 was used as a positive control to test for a NAb activity in mice intranasally immunized with gp120 or gp140 with IL-12 and Cholera Toxin B. Albu *et al.* [2003]
  - 2G12: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. 2G12 is able to neutralize both the wildtype and SOS protein comparably, but 2G12 could not neutralize SOS when added post-attachment. Binley *et al.* [2003] (**vaccine antigen design**)
  - 2G12: Crystal structure analysis of Fab 2G12 alone or complexed with Man $\alpha$ 1-2Man or Man9GlcNac2 demonstrates that the exchange of VH domains forms stable dimers for gp120 binding. Two Fabs assemble in an interlocked VH domain swapped dimer, providing an extended surface for multivalent interaction with the cluster of oligomannose on gp120, allowing high-affinity recognition of repeated epitopes in the carbohydrate structure. Ala substitutions of the 2G12 VH/VH' interface residues Ile H19, Arg H57, Phe H77, Tyr H80, Val H84 and Pro H113 result in the loss of 2G12-gp120 JR-FL binding. Calarese *et al.* [2003] (**antibody binding site definition and exposure, antibody sequence variable domain, structure**)
  - 2G12: The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. B4e8 and 2G12 enhanced each others binding, and gave synergistic neutralization. B4e8 could neutralize R5X4 virus 92HT593 better than 2G12, while 2G12 was better at neutralizing R5 virus 92US660. Cavacini *et al.* [2003] (**antibody interactions**)
  - 2G12: 2G12 was used as a negative control to investigate the relationship of MAb 412d epitope to the CCR5 binding site of gp120. These two MAbs were incubated with soluble CD4 and ADA gp120 in the presence of a peptide shown to block the association of gp120-CD4 with CCR5. As expected, the presence of the peptide did not inhibit precipitation of gp120 by 2G12, since it binds an epitope distinct from the CCR5 binding domain, while it did inhibit the 412d. Choe *et al.* [2003] (**antibody binding site definition and exposure**)
  - 2G12: A sCD4-17b single chain chimera was made that can bind to the CD4 binding site, then bind and block co-receptor interaction. This chimeric protein is a very potent neutralizing agent, more potent than IgG1b12, 2G12 or 2F5 against Ba-L infection of CCR5-MAGI cells. It has potential for prophylaxis or therapy. Dey *et al.* [2003] (**co-receptor**)
  - 2G12: Four newborn macaques were challenged with pathogenic SHIV 89.6 and given post exposure prophylaxis using a combination of NAbS 2F5, 2G12, 4E10 and IgG1b12. 2/4 treated animals did not show signs of infection, and 2/4 macaques maintained normal CD4+ T cell counts and had a lower delayed peak viremia compared to the controls. Ferrantelli *et al.* [2003] (**immunoprophylaxis, mother-to-infant transmission**)
  - 2G12: This study investigates the effects of glycosylation inhibitors on the binding between HIV-1 gp120 and mannose-binding lectin (MBL). Mannosidase I inhibitor deoxymannojirimycin (dMM) inhibits formation of complex and hybrid N-linked saccharides and yields virus with more mannose residues. dMM added during viral production significantly enhanced the binding 2F5 and 2G12, but not IgG1b12 in a viral capture assay. Hart *et al.* [2003] (**antibody binding site definition and exposure**)
  - 2G12: CD4BS MAbs b12 (neutralizing) and 205-42-15, 204-43-1, 205-46-9 (non-neutralizing) all cross-competed for binding to monomeric gp120, indicating the topological proximity of their epitopes, however, the non-neutralizing CD4BS MAbs did not interfere with the neutralization activity of MAb b12 – 2G12 was used to normalize and as a control in these experiments. Herrera *et al.* [2003] (**antibody interactions**)
  - 2G12: MAbs IgG1b12, 2G12, 2F5 and 4E10 were tested for their ability to neutralize two primary HIV-1 clade A isolates (UG/92/031 and UG/92/037) and two primary HIV-1 clade D isolates (UG/92/001 and UG/92/005). 4E10 demonstrated the most potent cross-neutralization activity. Quadruple administration of MAbs IgG1b12, 2G12, 2F5, and 4E10 induced strong synergistic neutralization of 4 clade A isolates (UG/92/031, UG/92/037, RW/92/020 and RW/92/025) as well as 5 clade D isolates (UG/92/001, UG/9/005, /93/086/RUG/94/108, UG/94/114). The authors note this combination of 4 MAbs neutralizes primary HIV A, B, C, and D isolates. Kitabwalla *et al.* [2003] (**antibody interactions, immunoprophylaxis, variant cross-recognition or cross-neutralization, mother-to-infant transmission, subtype comparisons**)
  - 2G12: Polyclonal Abs raised against soluble trivalently linked N35CCG-N13 and N34CCG, the internal trimeric core of the coiled-coil ectodomain, inhibit HIV-1 Env-mediated cell fusion at levels comparable to 2G12. Louis *et al.* [2003] (**vaccine antigen design**)
  - 2G12: This review discusses the importance and function of protective antibody responses in animal model studies in the context of effective vaccine development. SHIV models have shown protection using high levels of MAbs can prevent infection, and partial protection that can influence disease course can be obtained from modest levels of NAbS. SHIV challenges studies conducted with infusions of combinations of MAbs b12, 2G12, and 2F5 are reviewed. Mascola [2003] (**immunoprophylaxis, review**)
  - 2G12: Infusions of 2F5 and 2G12 intravenously administered 24h prior to vaginal SHIV-89.P challenge are able to protect macaques from infections. Animals that receive a IL-2 adjuvanted DNA immunization SIV Gag and HIV Env have T-cell

responses and lower viral loads, but were not protected. Sub-optimal levels of 2F5 and 2G12 were not able to confer sterile protection in combination with the T-cell responses stimulated by DNA immunizations. Mascola *et al.* [2003]

- 2G12: AC10 is a subject who was given treatment early after infection, and had a viral rebound after cessation of therapy, which then declined to a low level. The polyclonal sera from AC10 could potentially neutralize the rebound virus, and NAb escape followed with a neutralizing response against the escape variant and subsequent escape from that response. Viral loads remained low in this subject despite escape. The rebound isolate that was potentially neutralized by autologous sera was not particularly neutralization sensitive, as it resisted neutralization by sCD4 and MAbs IgG1b12, 2G12 and 2F5, and was only moderately sensitive to sera from other HIV+ individuals that had high titers of NAb to TCLA strains. Montefiori *et al.* [2003] (**acute/early infection, escape**)
- 2G12: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. 2G12 was the only MAb tested to recognize all blood and brain isolates from all four patients by gp120 immunoprecipitation. Ohagen *et al.* [2003] (**variant cross-recognition or cross-neutralization**)
- 2G12: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished – 2G12 binding was largely unperturbed, indicating these proteins were not grossly misfolded. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
- 2G12: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 2G12: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. CD4BS MAbs IgG1b12, F91 and F105 and their Fab counterparts (except for C11, used as a negative control) inhibited CD4-independent JR-FL and YU-2 gp120-CCR5 binding to CCR5-expressing Cf2Th cells and syncytium formation. The carbohydrate binding MAb 2G12 also inhibited CD4-independent syncytium formation. Raja *et al.* [2003] (**co-receptor**)
- 2G12: Most plasma samples of patients from early infection had NAb responses to early autologous viruses, and NAb against heterologous strains tended to be delayed. Serial plasma samples were tested against serial isolates, and neutralization escape was shown to be rapid and continuous throughout infection. Autologous neutralization-susceptible and resistant viruses from four patients were tested for susceptibility to neutralizing Ab responses using MAbs 2G12, IgG1b12 and 2F5. No correlation was established, all viruses tested were susceptible to at least one of the neutralizing MAbs. Two patients that did not have an autologous NAb response also did not evolve changes in susceptibility to these MAbs, while one patient with a pattern of autologous neutralization and escape acquired a 2G12 sensitive virus at month 6, and lost IgG1b12 sensitivity at month 21. Richman *et al.* [2003] (**autologous responses, acute/early infection, escape**)
- 2G12: To begin to design vaccine antigens that can mimic the carbohydrate structure, the gp120 peptide 336-342 was synthesized with Man(9), Man(6), and Man(5) moieties attached. Singh *et al.* [2003] (**vaccine antigen design**)
- 2G12: Review of current neutralizing antibody-based HIV vaccine candidates and strategies of vaccine design. Strategies for targeting of the epitopes for NAb 2F5, 2G12, 4E10, b12, and Z13 are described. They have shown that both N-glycans, at 295N and 332N are required for 2G12 binding, emphasizing the oligosaccharide cluster nature of the epitope, and suggest the uniqueness of the target structure may not result in autoimmune reactions. Wang [2003] (**vaccine antigen design, review**)
- 2G12: The broadly neutralizing antibodies 2F5 and 2G12 were class-switched from IgG to IgA and IgM isotypes. Neutralizing potency was increased with valence for 2G12 so the IgM form was most potent, but for 2F5 the IgG form was most potent. Eight primary isolates were tested including two subtype A isolates. The polymeric IgM and IgA Abs, but not the corresponding IgGs, could interfere with HIV-1 entry across a mucosal epithelial layer, although they were limited in a standard neutralization assay. All isotypes could interact with activated human sera, presumably through complement, to inhibit HIV replication. Wolbank *et al.* [2003] (**complement, isotype switch, variant cross-recognition or cross-neutralization, mucosal immunity, subtype comparisons**)
- 2G12: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. 2G12 had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- 2G12: A phase I trial in seven HIV+ individuals was conducted with MAbs 2F5 and 2G12 – no clinical or laboratory abnormalities were observed throughout the study – eight infusions were administered over a 4-week period (total dose 14 g) – the elimination half-life ( $t_{1/2}$ ) was calculated to be 7.94 (range, 3.46–8.31) days for 2F5 and 16.48 (range, 12.84–24.85) days for 2G12. Armbruster *et al.* [2002] (**kinetics, immunotherapy**)
- 2G12: IgG1b12 neutralized many South African (5/8) and Malawian (4/8) clade C primary HIV-1 isolates, being more effective than 2F5 which neutralized only two Malawian and no South African isolates. 2G12 did not neutralize any of the 16 isolates. Bures *et al.* [2002] (**subtype comparisons**)

- 2G12: This study examined Ab interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-gp41 MAb F240 did not affect binding of 2G12 to either R5X4 and R5 isolates, and anti-V3 MAb B4a1 increased 2G12 binding to R5X4 virions but not R5. Neutralization with B4a1 and 2G12 was additive for the R5X4 virus, and was enhanced for the R5 virus. Cavacini *et al.* [2002] (**antibody interactions, co-receptor, variant cross-recognition or cross-neutralization**)
- 2G12: A modified gp140 (gp140deltaCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation, retained antigenic conformational determinants as defined by binding to CD4 and to MAbs 2F5, 2G12, F105, and b12, and enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002] (**vaccine antigen design**)
- 2G12: Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**antibody binding site definition and exposure**)
- 2G12: Review of NABs that notes 2G12 alone or in combination with other MAbs can protect some macaques against SHIV infection, that it has strong ADCC activity, and that it is safe and well tolerated in humans. Ferrantelli & Ruprecht [2002] (**immunoprophylaxis**)
- 2G12: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)
- 2G12: UK1-br and MACS2-br are R5 isolates derived from brain tissue samples from AIDS patients with dementia and HIV-1 encephalitis; both are neurotropic, but only UK1-br induced neuronal apoptosis and high levels of syncytium formation in macrophages. UK1-br Env had a greater affinity for CCR5 than MACS-br, and required low levels of CCR5 and CD4 for cell-to-cell fusion and single round infection. PBMC infected with UK1-br and MACS2-br virus isolates were resistant to neutralization by MAb 2G12. UK1-br was more sensitive than MACS2-br to IgG1b12, 2F5 and CD4-IgG2 neutralization. Gorry *et al.* [2002] (**brain/CSF, co-receptor**)
- 2G12: HIV-1 gp160deltaCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines – 2F5 bound to gp160deltaCT with a reconstituted membrane ten-fold better than the same protein on beads, while such an affinity difference was not seen with F105 and 2G12 – anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160deltaCT PLs indistinguishably from gp160deltaCT expressed on the cell surface. Grundner *et al.* [2002] (**antibody binding site definition and exposure, vaccine antigen design**)
- 2G12: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, except for 2G12, which might not have bound well to the carbohydrate additions on the Drosophila expressed core. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. 2G12 had an entropy value of -1.6. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- 2G12: Review of NABs that discusses mechanisms of neutralization, passive transfer of NABs and protection in animal studies, and vaccine strategies. Liu *et al.* [2002] (**review**)
- 2G12: Rhesus macaques were better protected from vaginal challenge with SHIV89.6D (MAb 2G12, 2/4; MAbs 2F5/2G12, 2/5; and HIVIG/2F5/2G12, 4/5 infected) than from intravenous challenge (MAb 2G12, 0/3; MAbs 2F5/2G12, 1/3; and HIVIG/2F5/2G12, 3/6 infected) – the animals that were infected by vaginal challenge after Ab infusion had low or undetectable viral RNA levels and modest CD4 T-cell decline. Mascola [2002] (**immunoprophylaxis, mucosal immunity**)
- 2G12: The 2G12 epitope is composed of carbohydrates involving high-mannose and hybrid glycans of residues 295, 332, and 392, with peripheral glycans from 386 and 448 contributing on either flank, and with little direct gp120 protein surface involvement – these mannose residues are proximal to each other near the chemokine receptor binding surface. Sanders *et al.* [2002] (**antibody binding site definition and exposure**)
- 2G12: Alanine scanning mutagenesis used in conjunction with competition and replacement studies of N-linked carbohydrates and sugars suggest that the 2G12 epitope is formed from mannose residues contributed by the glycans attached to N295 and N332, with the other N-linked carbohydrates in positions N339, N386, and N392 playing a role in maintaining conformation relevant to 2G12 binding – N295A and N332A

mutants showed essentially unchanged anti-CD4BS NAb b12 binding affinities, while N339A, N386A and N392A mutants displayed significantly lowered b12 affinity, presumably due to conformational changes. Scanlan *et al.* [2002] (**antibody binding site definition and exposure**)

- 2G12: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140 – 2G12 complexes with SOS gp140 or with gp120 had a very unusual linear structure. Schulke *et al.* [2002] (**antibody binding site definition and exposure, vaccine antigen design**)
- 2G12: The antiviral response to intravenously administered MAbs 2F5 and 2G12 was evaluated in 7 HAART-naïve asymptomatic HIV-1 infected patients during a treatment period of 28 days. MAb therapy reduced plasma HIV RNA in 3/7 patients during the treatment period, and transiently reduced viral load in two more. CD4 counts were up in 3/7 through day 28, and transiently increased in three more. Vigorous complement activation was observed after 48/56 Ab infusions. Virus derived from 2/7 patients could be neutralized by 2G12, and escape from 2G12 was observed in both cases after infusion; one year after the infusion, isolates were again sensitive to 2G12. Stiegler *et al.* [2002] (**complement, variant cross-recognition or cross-neutralization, escape, immunotherapy**)
- 2G12: Passive immunization of neonate macaques with a combination of F105+2G12+2F5 conferred complete protection against oral challenge with SHIV-vpu+ or – the combination b12+2G12+2F5 conferred partial protection against SHIV89.6 – such combinations may be useful for prophylaxis at birth and against milk born transmission – the synergistic combination of IgG1b12, 2G12, 2F5, and 4E10 neutralized a collection of HIV clade C primary isolates. Xu *et al.* [2002] (**antibody interactions, immunoprophylaxis, mother-to-infant transmission**)
- 2G12: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibrin – stabilized oligomer gp140 delta683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and MAbs C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**antibody binding site definition and exposure**)
- 2G12: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**)
- 2G12: SF162DeltaV2 is a virus that has a 30 amino acids deletion in the V2 loop that does not abrogate its infectivity but renders it highly susceptible to neutralization – when incorporated into a codon-optimized DNA vaccine with a CMV promoter and delivered by gene gun, SF162DeltaV2 gave higher neutralizing Ab titers against SF162 than did SF162 itself, and Abs that cross-neutralized non-homologous primary isolates were obtained only when SF162DeltaV2, but not intact SF162, was used as the immunogen – Control MAbs 2F5 and 2G12 could neutralize all of the following primary isolates: 91US056(R5), 92US714(R5), 92US660(R5), 92HT593(R5X4), and BZ167(R5X4), while after the first protein boost, the sera from two SF162DeltaV2 immunized macaques could neutralize 91US056(R5), 92US714(R5), 92US660(R5) and ADA(R5), but not 92HT593(R5X4) or 92US657(R5) – the pattern of cross-recognition shifted after the second boost. Barnett *et al.* [2001] (**vaccine antigen design**)
- 2G12: A combination of MAbs IgG1b12, 2F5, and 2G12 was given postnatally to four neonates macaques that were then challenged with highly pathogenic SHIV89.6P – one of the four infants remained uninfected after oral challenge, two infants had no or a delayed CD4(+) T-cell decline. Hofmann-Lehmann *et al.* [2001] (**immunoprophylaxis, mother-to-infant transmission**)
- 2G12: Review of studies in macaques that have shown immune control of pathogenic SHIV viremia, improved clinical outcome, and protection, and the implications of the observations for HIV vaccines. Mascola & Nabel [2001] (**review**)
- 2G12: Moore and colleagues review structural aspects of gp120 and how they relate to antigenic domains, and review the data concerning the lack of a clear relationship between genetic subtype and serotype – an exception exists for human MAb 2G12, which does not recognize CRF01 envelopes because of an unusual additional disulfide bond in the V4 loop region that appears to be unique to the subtype E, CRF01 gp120 protein. Moore *et al.* [2001] (**antibody binding site definition and exposure, review**)
- 2G12: Structural aspects of the interaction of neutralizing Abs with HIV-1 Env are reviewed – Env essentially has three faces, one is largely inaccessible on the native trimer, and two that exposed but have low immunogenicity on primary viruses – neutralization is suggested to occur by inhibition of the interaction between gp120 and the target cell membrane receptors as a result of steric hindrance and it is noted that the attachment of approximately 70 IgG molecules per virion is required for neutralization, which is equivalent to about one IgG molecule per spike – the 2G12, 17b and b12 epitopes are discussed in detail – although it is potently neutralizing, 2G12 does not interfere with CD4 and coreceptor binding, and this Ab specificity is uncommon in sera from HIV-1-infected individuals. Poignard *et al.* [2001] (**antibody binding site definition and exposure, review**)
- 2G12: Chloroquine reduces the HIV-1-infectivity of H9 IIIB cells, apparently through altering the conformation of enve-

- lope – there is a reduction of reactivity of 2G12 to its epitope in chloroquine treated cultures. Savarino *et al.* [2001] (**antibody binding site definition and exposure**)
- 2G12: SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkey's yielded highly pathogenic SHIV KU-1 – HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160 – substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1 – 17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001]
  - 2G12: A luciferase-reporter gene-expressing T-cell line was developed to facilitate neutralization and drug-sensitivity assays – luciferase and p24 antigen neutralization titer end points were found comparable using NAb from sera from HIV+ donors, and MAbs 2F5, 2G12 and IgG1b12. Spenlehauer *et al.* [2001] (**assay development**)
  - 2G12: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**)
  - 2G12: Twenty HIV clade C isolates from five different countries were susceptible to neutralization by anti-clade B MAbs in a synergistic quadruple combination of mAbs IgG1b12, 2G12, 2F5, and 4E10. Xu *et al.* [2001] (**antibody interactions, variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 2G12: Neutralizing synergy between MAbs 1b12, 2G12 and 2F5 was studied using surface plasmon resonance to determine the binding kinetics for these three MAbs with respect to monomeric and oligomeric Env protein gp160 IIIB – the 2G12 epitope is highly accessible on both monomeric and oligomeric Envs, 1b12 is highly accessible on monomers but not oligomers, and 2F5 on neither form – binding of 2G12 exposes the 2F5 epitope on gp160 oligomers – 2G12-gp160 oligomer interactions were best fitted to a two state model, with the first complex having a high association constant and fast dissociation, stabilized by conformational changes induced by the binding of a second MAb. Zeder-Lutz *et al.* [2001] (**antibody binding site definition and exposure, antibody interactions, kinetics**)
  - 2G12: Neutralization synergy between anti-HIV NAb b12, 2G12, 2F5, and 4E10 was studied – a classic fixed-ratio method was used, as well as a method where one Ab was fixed at a low neutralization titer and the other was varied – using primary isolates, a two-four fold enhancement of neutralization was observed with MAb pairs, and a ten-fold enhancement with a quadruple Ab combination – no synergy was observed with any MAb pair in the neutralization of TCLA strain HXB2 – there was no evidence for cooperativity of binding between b12 and 2G12 to envelope spikes expressed on the cell surface of TCLA or primary isolates. Zwick *et al.* [2001c] (**antibody interactions**)
  - 2G12: A triple combination of 2F5, F105 and 2G12 effectively neutralized perinatal infection of macaque infants when challenged with SHIV-vpu+ – the mean plasma half-life was 14.0 +/- 7.9 days, the longest of the three Abs. Baba *et al.* [2000] (**immunoprophylaxis, mother-to-infant transmission**)
  - 2G12: To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**vaccine antigen design**)
  - 2G12: Because HIV-1 is most often transmitted across mucosal surfaces, the ability of passive transfer of infused HIVIG/2F5/2G12 to protect against mucosal exposure of macaques to pathogenic SHIV 89.6PD was studied – HIVIG/2F5/2G12 protected 4/5 animals against vaginal challenge, 2F5/2G12 combined protected 2/5 animals, and 2G12 alone protected 2/4 animals – in contrast, Mascola and co-workers had previously shown single MAbs could not protect against intravenous challenge – Ab treated animals that got infected through vaginal inoculation had low viral loads and only modest declines in CD4 counts – the infused Abs were detected in the nasal, vaginal, and oral mucosa. Mascola *et al.* [2000] (**immunoprophylaxis, mucosal immunity**)
  - 2G12: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – 2G12 was an exception and could not neutralize MN in either form. Park *et al.* [2000]
  - 2G12: A mini-review of observations of passive administration of IgG NAb conferring protection against intravenous or vaginal SHIV challenge, that considers why IgG MAbs might protect against mucosal challenge. Robert-Guroff [2000] (**immunoprophylaxis, mucosal immunity, review**)
  - 2G12: A Semliki Forest virus (SFV) expression system carrying BX08 Env was used to study the conformation of gp120 Env – intracytoplasmic gp120 was recognized by the anti-V3 MAbs K24 and F5.5, while gp120 at the plasma membrane was detected only by conformation dependent MAbs 2G12, 670-D and 694/98D and not V3 MAbs – expression in rat brain also showed that surface expressed Env was recognized only by the conformation-dependent Abs and not by anti-V3 Abs. Altmeyer *et al.* [1999]
  - 2G12: rgp120 derived from a R5X4 subtype B virus was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs – 2G12 was able to bind with low affinity to the rgp120 monomer HIV-1 W61D. Beddows *et al.* [1999]
  - 2G12: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by

NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**antibody binding site definition and exposure, vaccine antigen design**)

- 2G12: Neutralization assays with rsCD4, MAbs, and serum samples from SHIV-infected macaques and HIV-1 infected individuals were used to characterize the antigenic properties of the env glycoprotein of six primary isolate-like or TCLA SHIV variants. 2G12 neutralized the five SHIV strains tested, HXBc2, KU2, 89.6, 89.6P and KB9, in MT-2 cells. Crawford *et al.* [1999] (**variant cross-recognition or cross-neutralization**)
- 2G12: Combinations of HIVIG, 2F5, 2G12 were administered in passive-transfer experiments 24 hours prior to challenge with pathogenic SHIV 89.6PD – 3/6 animals given HIVIG/2F5/2G12 were completely protected, the others had reduced viremia and normal CD4 counts – 1/3 monkeys given 2F5/2G12 showed transient infection, the other two had reduced viral load – all monkeys that received HIVIG, 2F5, or 2G12 alone became infected and developed high-level plasma viremia, although animals that got HIVIG or 2G12 had a less profound CD4 T cell decline. Mascola *et al.* [1999] (**antibody interactions**)
- 2G12: A meeting summary presented results regarding neutralization – MAbs 2G12 and 2F5 tested for their ability to neutralize primary isolate infection of genetically engineered cell lines (cMAGI and others, presented by T. Matthews, A. Trkola, J. Bradac) – an advantage of such cell lines over PBMCs is that markers (X-Gal) can be added for staining to simplify the assay – the consensus of the meeting was that these engineered cell lines did not improve the sensitivity of detection of primary isolate neutralization – D. Burton and J. Mascola presented results concerning passive immunization and protection of hu-PBL-SCID mice and macaques, respectively, and both found combinations of MAbs that were able to achieve 99% neutralization *in vitro* corresponded to efficacy *in vivo*. Montefiori & Evans [1999] (**review**)
- 2G12: Review of the neutralizing Ab response to HIV-1. Parren *et al.* [1999] (**review**)
- 2G12: Hu-PBL-SCID mice were infected with HIV-1s JRCSF and SF162 to study the effect of NAbs on an established infection – no significant differences in the initial rate of decrease in viral load or the plateau levels of viral RNA between the b12 treated and control mice were seen – in most of the Ab treated mice b12 escape mutants were observed with varying patterns of mutations – a combination of b12, 2G12 and 2F5 protected 1/3 mice, and an isolate from one of the other two was resistant to neutralization by all three MAbs. Poignard *et al.* [1999] (**antibody interactions, escape**)
- 2G12: Post-exposure prophylaxis was effective when MAb 694/98-D was delivered 15 min post-exposure to HIV-1 LAI

in hu-PBL-SCID mice, but declined to 50% if delivered 60 min post-exposure, and similar time constraints have been observed for HIVIG, 2F5 and 2G12, in contrast to MAb BAT123 that could protect when delivered 4 hours post infection. Andrus *et al.* [1998] (**immunoprophylaxis**)

- 2G12: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – MAb 2G12 was the only exception to this, showing reduced binding efficiency. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
- 2G12: Ab from gp120 vaccinated individuals prior to infection, who subsequently became HIV infected, could not achieve 90% neutralization of the primary virus by which the individuals were ultimately infected – these viruses were not particularly refractive to neutralization, as determined by their susceptibility to neutralization by MAbs 2G12, IgG1b12, 2F5 and 447-52D. Connor *et al.* [1998]
- 2G12: Notes that 2G12 and 2F5, potent neutralizing antibodies, were identified by screening for cell surface (oligomeric Envelope) reactivity. Fouts *et al.* [1998] (**antibody binding site definition and exposure**)
- 2G12: Infection of dendritic cells cultured from CD14+ blood cells or from cadaveric human skin was blocked by neutralizing MAbs IgG1b12, or 2F5 and 2G12 delivered together, but not by control non-neutralizing anti-gp120 MAb 4.8D, indicating that NAbs could interrupt early mucosal transmission events. Frankel *et al.* [1998] (**mucosal immunity**)
- 2G12: The complete V, J and D(H) domain was sequenced – unlike non-neutralizing anti-gp41 MAb 3D6, five neutralizing MAbs (2F5, 2G12, 1B1, 1F7, and 3D5) showed extensive somatic mutations giving evidence of persistent antigenic pressure over long periods – 2G12 D(H) has the best homology to a D(H) segment between D3-22 and D4-23, a region not usually considered for heavy-chain rearrangement because it lacks associated recombination signals in the flanking regions, Kunert *et al.* suggest this may be why Abs that compete with 2G12 are rare. Kunert *et al.* [1998] (**antibody sequence variable domain**)
- 2G12: Neutralization synergy was observed when the MAbs 694/98-D (V3), 2F5 (gp41), and 2G12 (gp120 discontinuous) were used in combination, and even greater neutralizing potential was seen with the addition of a fourth MAb, F105 (CD4 BS). Li *et al.* [1998] (**antibody interactions**)
- 2G12: Enhances Hx10 binding to CD4 positive or negative HeLa cells, but inhibited binding to CD4+ T-cell line A3.01 – neutralizes Hx10 infection of the HeLa cells. Mondor *et al.* [1998]
- 2G12: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- 2G12: MAbs 2G12, 2F5 and b12 are broadly neutralizing, as are some human polyclonal sera, but this paper describes a set of primary isolates that are resistant to all three MAbs and

- 2 broadly neutralizing sera – results indicate that resistance levels of pediatric isolates might be higher than adult isolates – resistance in general did not seem to be conferred by a loss of binding affinity for gp120 or gp41, rather by a more global perturbation of oligomeric Envelope. Parren *et al.* [1998b] (**variant cross-recognition or cross-neutralization**)
- 2G12: In a study of the influence of the glycan at position 306 of the V3 loop on MAb recognition, 2G12 was found to neutralize an HIV-BRU mutant virus that lacks the V3 loop glycan and has a mutation at the tip of the loop more efficiently than it neutralizes HIV-BRU. Schonning *et al.* [1998] (**antibody binding site definition and exposure**)
  - 2G12: Does not compete with binding of MAb generated in response to gp120-CD4 complex, CG10. Sullivan *et al.* [1998b] (**antibody interactions**)
  - 2G12: Induces complement-mediated lysis in MN but not primary isolates – primary isolates are refractive to CML. Takefman *et al.* [1998] (**complement, variant cross-recognition or cross-neutralization**)
  - 2G12: A wide range of neutralizing titers was observed that was independent of co-receptor usage. Trkola *et al.* [1998] (**co-receptor, variant cross-recognition or cross-neutralization**)
  - 2G12: Summary of the implications of the crystal structure of gp120 combined with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by 2G12 is unknown, but dependent on proper glycosylation and 2G12 is predicted to be oriented toward the target cell when bound, so neutralization may be due to steric hindrance – mutations in positions N 295, T 297, S 334, N 386, N 392 and N 397 HXBc2 (IIIB) decrease 2G12 binding, and the binding region is 25 angstroms from the CD4 binding site – probably the Ab binds in part to carbohydrates, which may account for both its broad reactivity and the scarcity of Abs in the same competition group. Wyatt *et al.* [1998] (**antibody binding site definition and exposure**)
  - 2G12: Review of the antigenic and receptor binding-domains of gp120 in relation to the structure of the molecule – MAbs are discussed by category (anti-V2, anti-V3, CD4i, CD4BS...), however as 2G12 binds to a rarely immunogenic region, and it is dependent on glycosylation, it was discussed individually. Wyatt & Sodroski [1998] (**review**)
  - 2G12: Review that discusses this MAb – reacts with residues at the base of the V3 loop and V4, and most of the changes that reduce binding are glycosylation sites – it is not clear whether the binding site is peptidic or direct carbohydrate. Burton & Montefiori [1997] (**antibody binding site definition and exposure, review**)
  - 2G12: In a multilab evaluation of monoclonal antibodies, only IgG1b12, 2G12, and 2F5 could neutralize at least half of the 9 primary test isolates at a concentration of < 25 mug per ml for 90% viral inhibition – neutralized 6 of 9 primary isolates. D'Souza *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
  - 2G12: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 2G12 bound monomer, and weakly bound oligomer and neutralized JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
  - 2G12: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB Env – 2G12 was a strong neutralizer of SHIV-vpu+ – all Ab combinations tested showed synergistic neutralization – 2G12 has synergistic response with MAbs 694/98-D (anti-V3), 2F5, F105, and b12. Li *et al.* [1997] (**antibody interactions**)
  - 2G12: Using concentrations of Abs achievable *in vivo*, the triple combination of 2F5, 2G12 and HIVIG was found to be synergistic to have the greatest breadth and magnitude of response against 15 clade B primary isolates. Mascola *et al.* [1997] (**antibody interactions, variant cross-recognition or cross-neutralization**)
  - 2G12: A JRCSF variant that was selected for IgG1b12 resistance remained sensitive to MAbs 2G12 and 2F5, for combination therapy. Mo *et al.* [1997] (**escape**)
  - 2G12: Review: MAbs 2F5, 2G12 and IgG1b12 have potential for use in combination with CD4-IgG2 as an immunotherapeutic or immunoprophylactic – homologous MAbs to these are rare in humans and vaccine strategies should consider including constructs that may enhance exposure of these MAbs' epitopes. Moore & Trkola [1997] (**immunoprophylaxis, immunotherapy, review**)
  - 2G12: Neutralizes TCLA strains and primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
  - 2G12: Viral binding inhibition by 2G12 was strongly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5). Ugolini *et al.* [1997] (**antibody binding site definition and exposure**)
  - 2G12: Neutralizes primary isolates, HXB2, and chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
  - 2G12: Binding weakly enhanced by some anti-C1, -C4, -V3, and CD4 binding site MAbs – unusual in that 2G12 binding neither enhanced or inhibited the binding of other MAbs included in the study. Moore & Sodroski [1996] (**antibody interactions**)
  - 2G12: Review: exceptional capacity to neutralize primary isolates in terms of both breadth and potency – one of three MAbs (IgG1b12, 2G12, and 2F5) generally accepted as having significant potency against primary isolates. Pognard *et al.* [1996b] (**variant cross-recognition or cross-neutralization, review**)
  - 2G12: Review: Only four epitopes have been described which can stimulate a useful neutralizing response to a broad spectrum of primary isolates, represented by the binding sites of MAbs: 447-52-D, 2G12, Fab b12, and 2F5. Sattentau [1996] (**review**)
  - 2G12: Conformationally sensitive epitope destroyed by mutations altering the N-linked glycosylation sites near the base of the V3 loop and the amino-terminal flank of the V4 loop. Trkola *et al.* [1996b] (**antibody binding site definition and exposure**)
  - 2G12: Neutralizes JR-FL – inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**co-receptor**)

- 2G12: Review: binding site is distinct from CD4BS MAbs epitope and is unique among known gp120 MAbs, human or rodent. Moore & Ho [1995] (**review**)
- 2G12: Highly potent Cross-clade neutralizing activity. Trkola *et al.* [1995] (**subtype comparisons**)
- 2G12: Human MAb generated by electrofusion of PBL from HIV-1 + volunteers with CB-F7 cells. Buchacher *et al.* [1994] (**antibody generation**)

**No.** 827  
**MAb ID** 30D  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)**

**References** Yang *et al.* 2002

- 30D: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibrin—stabilized oligomer gp140Δ683(-FT) showed strong preferential recognition by NAb IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002]

**No.** 828  
**MAb ID** 31710B  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing**  
**Immunogen**

**Species (Isotype)** human (IgG1)

**References** Alsmadi & Tilley 1998

- 31710B: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against all four strains. Alsmadi & Tilley [1998]

**No.** 829  
**MAb ID** 38B5/C9  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)

**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 38B5/C9: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—38B5/C9 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

**No.** 830  
**MAb ID** 39H10/A11  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)

**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 39H10/A11: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—39H10/A11 bound to three R5 and three X4 B clade viruses, as well as two E clade viruses. He *et al.* [2002]

**No.** 831  
**MAb ID** 3C9  
**HXB2 Location** Env  
**Author Location** gp120

**Epitope**  
**Subtype** B  
**Neutralizing** L  
**Immunogen** vaccine

*Strain:* B clade SF2

**Species (Isotype)** mouse

**References** Kang *et al.* 1992

**Keywords** anti-idiotypic, vaccine antigen design, variant cross-recognition or cross-neutralization

- C39: Murine antibodies were raised against human polyclonal antibodies against gp120, pooled from HIV-1 infected individuals. One anti-idiotypic MAb was shown to bind to the CD4-binding site, and this MAb could raise anti-anti-idiotypic antibodies when injected into cynomolgous monkeys. The monkey MAbs neutralized laboratory strains MN, RF, and IIIB.



Kang *et al.* [1992] (**anti-idiotypic, vaccine antigen design, variant cross-recognition or cross-neutralization**)

No. 832

MAb ID 3D5

HXB2 Location Env

Author Location Env

Epitope

Neutralizing L

Immunogen HIV-1 infection

Species (Isotype) human

Research Contact Herman Katinger, Inst. Appl. Microbiol. University of Agricultural Science, Vienna, Austria

References Kunert *et al.* 1998; Purtscher *et al.* 1994; Buchacher *et al.* 1994

- 3D5: The complete V, J and D(H) domain was sequenced – unlike non-neutralizing anti-gp41 MAb 3D6, five neutralizing MAbs (2F5, 2G12, 1B1, 1F7, and 3D5) showed extensive somatic mutations giving evidence of persistent antigenic pressure over long periods. Kunert *et al.* [1998]
- 3D5: Generated by electrofusion of PBL from HIV-1 positive volunteers with CB-F7 cells. Buchacher *et al.* [1994]

No. 833

MAb ID 3H6

HXB2 Location Env

Author Location gp41

Epitope

Neutralizing

Immunogen

Species (Isotype) mouse

References Pinter *et al.* 1995

- 3H6 database comment: There is another MAb with this ID that recognizes Rev.
- 3H6: Generated in response to virus grown in protein-free medium. Pinter *et al.* [1995]

No. 834

MAb ID 4.11C

HXB2 Location Env

Author Location

Epitope

Neutralizing

Immunogen

Species (Isotype) human

Ab Type gp120 adjacent to CD4BS

References Haynes *et al.* 2005

Keywords antibody binding site definition and exposure

- 4.11C: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 4.11C has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 835

MAb ID 4.6H

HXB2 Location Env

Author Location

Epitope

Neutralizing

Immunogen

Species (Isotype) human

Ab Type gp120 adjacent to CD4BS

References Haynes *et al.* 2005

Keywords antibody binding site definition and exposure

- 4.6H: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 4.6H has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 836

MAb ID 4.8E

HXB2 Location Env

Author Location

Epitope

Neutralizing

Immunogen

Species (Isotype) human

Ab Type gp120 CCR5BS

References Haynes *et al.* 2005

Keywords antibody binding site definition and exposure

- 4.8E: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 4.8E has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 837

MAb ID 40D3/C11

HXB2 Location Env

Author Location gp120 (SF162)

Epitope

Subtype B

Neutralizing no

Immunogen vaccine

Vector/Type: protein Strain: B clade SF162

HIV component: gp120 Adjuvant: Ribi adjuvant (MPL+TDM) (RIBI)

Species (Isotype) transgenic mouse (IgG2κ)

Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

References He *et al.* 2002

- 40D3/C11: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were

part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—40D3/C11 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

**No.** 838  
**MAb ID** 412d  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**  
**Ab Type** gp120 CD4i, gp120 CCR5BS  
**References** Dorfman *et al.* 2006; Choe *et al.* 2003  
**Keywords** antibody binding site definition and exposure, co-receptor, neutralization

- 412d: The CDR3 regions of CD4i Abs (E51, 412d, 17b, C12 and 47e) were cloned onto human IgG1 and tested for their ability to inhibit CCR5 binding. Only E51 successfully immunoprecipitated gp120. Dorfman *et al.* [2006] (**co-receptor**)
- 412d: 412d was obtained from an HIV-1 infected individual with a potent ELISA response to the gp120. It was shown that this MAb heavy chain is sulfate-modified. The sulfates of 412d were present exclusively on tyrosines of its heavy chain CDR3 and they contributed to the binding of this MAb to the gp120 of at least three primary HIV isolates. Binding efficiency of 412d to ADA gp120 was doubled in the presence of CD4, showing that this MAb is a CD4-induced. Association of 412d with ADA gp120-CD4-Ig complex was partially inhibited by a sulfated peptide with a sequence corresponding to the CCR5 amino terminus, indicating that 412d binds a CD4-enhanced epitope overlapping the binding domain of CCR5 amino terminus. Neutralization assays showed that 412d neutralizes primary R5 and R5X4 isolates more efficiently, and X4 isolates less efficiently, than CD4i Abs 17b and 48d. Furthermore, 412d scFv was more than 10 times as potent as full-length 412d at neutralizing ADA. scFv 412d was shown to efficiently bind to gp120 of three R5 isolates but not to the HXBc2 X4 isolate. Choe *et al.* [2003] (**antibody binding site definition and exposure, co-receptor, neutralization**)

**No.** 839  
**MAb ID** 47e  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**  
**Ab Type** gp120 CD4i, gp120 CCR5BS  
**References** Dorfman *et al.* 2006; Choe *et al.* 2003  
**Keywords** antibody binding site definition and exposure, co-receptor

- 47e: The CDR3 regions of CD4i Abs (E51, 412d, 17b, C12 and 47e) were cloned onto human IgG1 and tested for their ability to inhibit CCR5 binding. Only E51 successfully immunoprecipitated gp120. Dorfman *et al.* [2006] (**co-receptor**)

- 47e: 47e was obtained from an HIV-1 infected individual with a potent ELISA response to the gp120. It was shown that this MAb heavy chain is sulfate-modified and that the sulfation is dependent upon a single tyrosine in its heavy chain CDR3. The sulfate on 47e was shown to substantially contribute to this MAb's ability to bind ADA, but not YU2, envelope glycoprotein. Binding efficiency of 47e to ADA gp120 was doubled in the presence of CD4, showing that this MAb is a CD4-induced. Association of 47e with ADA gp120-CD4-Ig complex was partially inhibited by a sulfated peptide with a sequence corresponding to the CCR5 amino terminus, indicating that 47e binds a CD4-enhanced epitope overlapping the binding domain of CCR5 amino terminus. Choe *et al.* [2003] (**antibody binding site definition and exposure, co-receptor**)

**No.** 840  
**MAb ID** 49B11/A1  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** transgenic mouse (IgG2κ)  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org  
**References** He *et al.* 2002

- 49B11/A1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—49B11/A1 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

**No.** 841  
**MAb ID** 52G5/B9  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** transgenic mouse (IgG2κ)  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org  
**References** He *et al.* 2002

- 52G5/B9: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2 $\kappa$  MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—52G5/B9 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

**No.** 842  
**MAb ID** 55E4/H1  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2 $\kappa$ )  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 55E4/H1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2 $\kappa$  MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—55E4/H1 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

**No.** 843  
**MAb ID** 56C4/C8  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2 $\kappa$ )  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 56C4/C8: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2 $\kappa$  MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with

HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—56C4/C8 bound to some R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

**No.** 844  
**MAb ID** 570-D  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** (IgG1 $\lambda$ )  
**Ab Type** gp120 CD4BS  
**References** Holl *et al.* 2006a  
**Keywords** dendritic cells, neutralization

- 570-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)

**No.** 845  
**MAb ID** 57B6/F1  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2 $\kappa$ )  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 57B6/F1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2 $\kappa$  MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—57B6/F1 bound some R5 and X4 B clade viruses, and no E clade viruses. He *et al.* [2002]

**No.** 846  
**MAb ID** 57H5/D7  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 57H5/D7: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—57H5/D7 bound to most R5 and X4 B clade viruses, as well as one of two E clade viruses. He *et al.* [2002]

**No.** 847

**MAb ID** 5E

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- 5E: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 5E has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

**No.** 848

**MAb ID** 63G4/E2

**HXB2 Location** Env

**Author Location** gp120 (SF162)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 63G4/E2: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with

HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—63G4/E2 bound to three R5 and three X4 B clade viruses, as well as two E clade viruses. He *et al.* [2002]

**No.** 849

**MAb ID** 65B12/C5

**HXB2 Location** Env

**Author Location** gp120 (SF162)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 65B12/C5: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—11 of the MAbs were conformation dependent, but did not block sCD4 binding—these MAbs were part of the same competition group, and enhanced binding of the CD4BS MAb 38G3/A9 and anti-CD4BS MAbs also enhanced their binding—these MAbs tended to be very cross-reactive but could not neutralize autologous SF162—65B12/C5 bound some R5 and X4 B clade viruses, and no E clade viruses. He *et al.* [2002]

**No.** 850

**MAb ID** 694/98D

**HXB2 Location** Env

**Author Location** Env (LAI)

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Ling *et al.* 2004

**Keywords** antibody binding site definition and exposure

- 694-98D: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of the V3 MAb 694-98D to its epitope was decreased by both thrombin and trypsin. Ling *et al.* [2004] (**antibody binding site definition and exposure**)

**No.** 851

**MAb ID** 6D8

**HXB2 Location** Env

**Author Location** gp120 (21–85)

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)**

**Research Contact** Phil Berman

**References** Callahan *et al.* 1991

- 6D8: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interactions mediated through the local high positive charge density in the V3 loop. The binding of this N-term binding antibody is increased by dextran sulfate, in contrast to anti-V3 antibodies that are inhibited. Callahan *et al.* [1991]

**No.** 852

**MAb ID** 6E10

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen**

**Species (Isotype)**

**Research Contact** Phil Berman

**References** Callahan *et al.* 1991; Berman *et al.* 1991

- Isolation of antibody. Berman *et al.* [1991]
- 6E10: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interactions mediated through the local high positive charge density in the V3 loop. The binding of this antibody is not inhibited by dextran sulfate, in contrast to anti-V3 antibodies. Callahan *et al.* [1991]

**No.** 853

**MAb ID** 7-1054

**HXB2 Location** Env

**Author Location** gp36 (HIV-2)

**Epitope**

**Neutralizing** no

**Immunogen**

**Species (Isotype)** mouse

**References** Scheffel *et al.* 1999

- Binds HIV-2 gp36, used as a control in a study of group O MAbs. Scheffel *et al.* [1999]

**No.** 854

**MAb ID** 8.2A

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 C1-C4

**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- 8.2A: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 8.2A has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

**No.** 855

**MAb ID** 85G11/D8

**HXB2 Location** Env

**Author Location** gp120 (SF162)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162

*HIV component:* deglycosylated gp120

*Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 85G11/D8: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—three of the MAbs were conformation dependent, but did not block sCD4 binding and were part of the same competition group—these MAbs were all raised against a deglycosylated form of gp120—they could not neutralize autologous SF162 and bound some R5 and X4 B clade viruses, and no E clade viruses. He *et al.* [2002]

**No.** 856

**MAb ID** 87E4/A8

**HXB2 Location** Env

**Author Location** gp120 (SF162)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162

*HIV component:* deglycosylated gp120

*Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 87E4/A8: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—three of the MAbs were conformation dependent, but did not block sCD4 binding and were part of the same competition group—these MAbs were all raised against

a deglycosylated form of gp120—they could not neutralize autologous SF162 and bound some R5 and X4 B clade viruses, and no E clade viruses. He *et al.* [2002]

**No.** 857  
**MAb ID** 97B1/E8  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* deglycosylated gp120  
*Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** transgenic mouse (IgG2κ)  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** He *et al.* 2002

- 97B1/E8: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—three of the MAbs were conformation dependent, but did not block sCD4 binding and were part of the same competition group—these MAbs were all raised against a deglycosylated form of gp120—they could not neutralize autologous SF162 and bound some R5 and X4 B clade viruses, and no E clade viruses. He *et al.* [2002]

**No.** 858  
**MAb ID** A9  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* GM-CSF  
**Species (Isotype)** mouse (IgG1)  
**References** del Real *et al.* 1999

- A9: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – A9 was a gp120 from a BALBc reconstructed nude mouse and had VH gene 7183-2. del Real *et al.* [1999]

**No.** 859  
**MAb ID** ADP421 polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** A

**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120

**Species (Isotype)** rabbit

**References** Jeffs *et al.* 2004

- Keywords** subtype comparisons, vaccine antigen design
- ADP421: A set of oligomeric envelope proteins were made from six primary isolates for potential use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. ADP421 is a polyclonal rabbit sera raised against CHO-derived IIIB gp120. ADP421 bound to antigens from all clades A-F, as well as group O. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design, subtype comparisons**)

**No.** 860  
**MAb ID** AG10H9  
**HXB2 Location** Env  
**Author Location** gp41 (717–751)

**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**

**Research Contact** BabCO

**References** Ohagen *et al.* 2003

- Keywords** brain/CSF, variant cross-recognition or cross-neutralization
- AG10H9: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. AG10H9 recognized most variants gp41 and gp160 from 3/4 individuals by WB, but not the 4th. Ohagen *et al.* [2003] (**brain/CSF, variant cross-recognition or cross-neutralization**)

**No.** 861  
**MAb ID** AH48  
**HXB2 Location** Env  
**Author Location** gp120 (V3)

**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human

**References** Zwick *et al.* 2003

- Keywords** antibody generation, antibody interactions
- AH-48: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS.

MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. AH48 is a novel anti-V3 Fab first used in this study. Zwick *et al.* [2003] (**antibody generation, antibody interactions**)

**No.** 862  
**MAB ID** B4  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120

**Species (Isotype)** mouse (IgM)

**References** del Real *et al.* 1999

- B4: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – B4 was an anti-gp120 from a BALBc reconstructed nude mouse and had VH gene J606. del Real *et al.* [1999]

**No.** 863  
**MAB ID** B5  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* GM-CSF

**Species (Isotype)** mouse (IgG1)

**References** del Real *et al.* 1999

- B5: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – B5 was a gp120 specific MAb from a BALBc mouse and had VH gene J558. del Real *et al.* [1999]

**No.** 864  
**MAB ID** B6  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine

*Vector/Type:* chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120

**Species (Isotype)** mouse (IgM)

**References** del Real *et al.* 1999

- B6: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – B6 was a gp120 from a BALBc reconstructed nude mouse and had VH gene J558. del Real *et al.* [1999]

**No.** 865  
**MAB ID** BAT267  
**HXB2 Location** Env  
**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1)

**References** Fung *et al.* 1987

**No.** 866  
**MAB ID** BAT401  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1)

**References** Fung *et al.* 1987

**No.** 867  
**MAB ID** BAT509  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* inactivated HIV *Strain:* B clade IIIB *HIV component:* HIV-1

**Species (Isotype)** mouse (IgG1)

**References** Fung *et al.* 1987

**No.** 868  
**MAB ID** C02-17  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4i

**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-17: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-17 was identified only by yeast display, and is a CD4i antibody. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

**No.** 869

**MAb ID** C02-19

**HXB2 Location** Env

**Author Location** gp120 (JR-FL)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4i

**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-19: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-19 was identified using only yeast display, and is a CD4i antibody; C02-19 and D02-33 have the same VH sequence. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

**No.** 870

**MAb ID** C02-34

**HXB2 Location** Env

**Author Location** gp120 (JR-FL)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 V3

**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-34: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-34 was identified only by yeast display, and it binds to V3. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

**No.** 871

**MAb ID** C02-41

**HXB2 Location** Env

**Author Location** gp120 (JR-FL)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4BS

**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-41: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-41 was identified using both methods, and binds to the CD4BS. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

**No.** 872

**MAb ID** C02-53

**HXB2 Location** Env

**Author Location** gp120 (JR-FL)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4i

**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity



- C02-53: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-53 was identified only by yeast display, and is a CD4i antibody; C02-53 and D02-7 have the same VH sequence. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

**No.** 873  
**MAb ID** C02-7  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 CD4i  
**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C02-7: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C02-7 was identified only by yeast display, and is a CD4i antibody. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

**No.** 874  
**MAb ID** C18-2  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 CD4BS  
**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- C18-2: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were

compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. C18-2 was identified only by yeast display, and it binds to the CD4 binding site. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

**No.** 875  
**MAb ID** C31  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**References** Boyer *et al.* 1991

- C31: Broadly-reactive group specific MAb – high yield cultivation of human MAb. Boyer *et al.* [1991]

**No.** 876  
**MAb ID** CM51  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**

**References** Choe *et al.* 2003

**Keywords** antibody binding site definition and exposure

- CM51: CM51 was obtained from an HIV-1 infected individual with a potent ELISA response to the gp120. It was shown that this MAb heavy chain is sulfate-modified. Choe *et al.* [2003] (**antibody binding site definition and exposure**)

**No.** 877  
**MAb ID** CO11  
**HXB2 Location** Env  
**Author Location** gp120 (V3)  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**  
**Ab Type** gp120 V3  
**Research Contact** James Robinson, Tulane University, New Orleans, LA, USA  
**References** Haynes *et al.* 2005; Pantophlet *et al.* 2004; Grundner *et al.* 2002

**Keywords** antibody binding site definition and exposure, vaccine antigen design

- CO11: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. CO11 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

- CO11: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only 3 additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including CO11. Pantophlet *et al.* [2004] (**vaccine antigen design**)

No. 878  
**MAb ID** D02-1  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 CD4i  
**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-1: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-1 was identified only using yeast display, and is a CD4i antibody with an affinity increase of 2-5 fold when sCD4 is present. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

No. 879  
**MAb ID** D02-20  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 CD4BS  
**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-20: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were

compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-20 was identified using both methods, and binds to the CD4BS. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

No. 880  
**MAb ID** D02-24  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 CD4i  
**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-24: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-24 was identified only by yeast display, and is a CD4i antibody. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

No. 881  
**MAb ID** D02-3  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**References** Bowley *et al.* 2007

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-3: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-3 was identified only by yeast display, and its binding site is unknown. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

No. 882  
**MAb ID** D02-33  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 CD4i  
**References** Bowley *et al.* 2007  
**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-33: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-33 was identified using only yeast display, and is a CD4i antibody; C02-19 and D02-33 have the same VH sequence. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

No. 883  
**MAb ID** D02-34  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 CD4i  
**References** Bowley *et al.* 2007  
**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-34: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-34 was identified only by yeast display, and is a CD4i antibody. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

No. 884  
**MAb ID** D02-6  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)  
**Epitope**

**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 CD4BS  
**References** Bowley *et al.* 2007  
**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-6: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-6 was identified using both methods, and binds to the CD4BS. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

No. 885  
**MAb ID** D02-7  
**HXB2 Location** Env  
**Author Location** gp120 (JR-FL)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 CD4i  
**References** Bowley *et al.* 2007  
**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity

- D02-7: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. D02-7 was identified only by yeast display, and is a CD4i antibody; C02-53 and D02-7 have the same VH sequence. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)

No. 886  
**MAb ID** D1  
**HXB2 Location** Env  
**Author Location** gp41 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140  
**Species (Isotype)** mouse (IgG)

**References** Otteken *et al.* 1996

- D1: MAbs D1, D16, had T37 bind to oligomeric gp160 equally well – pulse label experiments of MAb binding to non-cleavable gp160 revealed that these MAbs bound with a delay, epitopes forming with a half-life of 30 min. Otteken *et al.* [1996]

No. 887

**MAb ID** D12**HXB2 Location** Env**Author Location** gp41 (IIIB)**Epitope****Neutralizing** L**Immunogen** vaccine*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140**Species (Isotype)** mouse (IgG)**Research Contact** Patricia Earl and Christopher Broder, NIH**References** Yang *et al.* 2000; LaBranche *et al.* 1999; Otteken *et al.* 1996; Earl *et al.* 1997; Richardson *et al.* 1996; Broder *et al.* 1994; Earl *et al.* 1994**Keywords** antibody binding site definition and exposure, antibody generation, antibody interactions, vaccine antigen design

- D12: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – gp41 MAbs T4, D12, T3, and D50 bound less efficiently to gp140-GNC4 than did pooled sera, but T4 and D12 recognized the gp140-GNC4 trimer equivalently to gp140(-), and T3 and D50 recognized the trimer at greater levels than gp140(-). Yang *et al.* [2000] (**vaccine antigen design**)
- D12: D12 was used in WB of HIV-1 transmembrane proteins in a study which showed that determinants of HIV-1 CD4 independence map outside regions required for coreceptor specificity – IIIBx, a CD4-independent variant of IIIB, has a truncated gp41. LaBranche *et al.* [1999]
- D12: MAbs D10 and D12 are very easily blocked by human sera from HIV+ individuals. Earl *et al.* [1997]
- D12: MAbs D4, D10, D11, D12, and D41 all bind only to complete oligomer – pulse label experiments of MAb binding to noncleavable gp160 revealed that these MAbs bound with a delay, epitopes forming with a half life of 30 min. Otteken *et al.* [1996] (**antibody binding site definition and exposure**)
- D12: This antibody was blocked more strongly by human sera than other anti-gp41 MAbs (D20, D43, D61, and T4) in a oligomeric ELISA assay. Richardson *et al.* [1996] (**antibody interactions**)
- D12: One of 18 MAbs (e. g. D4 and D40) that bind to a conformation-dependent epitope in gp41 that bind preferentially, but not exclusively, to oligomers – neutralizes IIIB and SF2. Broder *et al.* [1994] (**antibody binding site definition and exposure**)
- D12: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 888

**MAb ID** D16**HXB2 Location** Env**Author Location** gp41 (IIIB)**Epitope****Neutralizing** L**Immunogen** vaccine*Vector/Type:* protein *HIV component:* dimeric Env**Species (Isotype)** mouse (IgG)**Research Contact** Patricia Earl and Christopher Broder, NIH**References** Earl *et al.* 1997; Weissenhorn *et al.* 1996; Earl *et al.* 1994

- D16: One of eleven MAbs (D16, D17, D31, D36, D37, D40, D44, D55, D59, T37, and T45) that are conformation dependent and that can block the binding of the MAb D50 that binds to the linear peptide gp41(642-665) – reactive with 9/10 HIV-1 strains all except HIV-1 ADA, which has the change E659D and E662A that may result in the loss of binding (ELLE to DLLA). Earl *et al.* [1997]
- D16: Precipitates both oligomeric gp140 and soluble monomeric gp41(21-166) that lacks the fusion peptide and membrane anchor, along with MAbs D16, D38, D40, D41, and D54. Weissenhorn *et al.* [1996]
- D16: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 889

**MAb ID** D4**HXB2 Location** Env**Author Location** gp120 (IIIB)**Epitope****Neutralizing****Immunogen** vaccine*Vector/Type:* chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120**Species (Isotype)** mouse (IgG1)**References** del Real *et al.* 1999

- D4: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – D4 was a gp120 from a BALBc reconstructed nude mouse and had VH gene J558. del Real *et al.* [1999]

No. 890

**MAb ID** D43**HXB2 Location** Env**Author Location** gp41 (HXB2)**Epitope****Subtype** B**Neutralizing****Immunogen** vaccine*Vector/Type:* protein *HIV component:* dimeric Env**Species (Isotype)** mouse (IgG)**Research Contact** Patricia Earl and Christopher Broder, NIH

**References** Earl *et al.* 1997; Richardson *et al.* 1996; Earl *et al.* 1994

- D43: Partially conformation dependent – doesn't bind to short peptides, but does bind to the region spanning 641-683 – binding can be blocked by MAbs T3, D38 and D45 – MAbs in this competition group reacted with 9/10 HIV-1 strains, not binding to JRFL. Earl *et al.* [1997]
- D43: This is a linear gp41 epitope, mapping in the region 635-678 – human sera blocked binding in oligomeric ELISA assay to a similar extent for gp41 MAbs D20, D43, D61, and T4. Richardson *et al.* [1996]
- D43: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 891

**MAb ID** E047

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CCR5BS

**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- E047: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. E047 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 892

**MAb ID** E2E

**HXB2 Location** Env

**Author Location** gp140 (WHO-15\_28)

**Epitope**

**Subtype** D

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* gp140 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** mouse

**References** Billington *et al.* 2007

**Keywords** antibody generation

- 2E2: The T30 antibody was used to partially purify a D subtype rgp140 that forms a stable trimer and may be suitable for structural studies. The partially purified protein was used to immunize mice, and one of the MAbs obtained from the immunized mice, 2E2, was used for further immunoaffinity purification the protein. Billington *et al.* [2007] (**antibody generation**)

No. 893

**MAb ID** ED10

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CCR5BS

**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- ED10: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. ED10 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 894

**MAb ID** EH21

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 C1-C4

**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- EH21: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. EH21 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 895

**MAb ID** F1

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Haynes *et al.* 2005; Fujii *et al.* 1993

- F1: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. F1 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005]
- F1 database note: There is a Nef (Fujii1993) and a CD4BS (Haynes2005) MAb that are called F1. Fujii *et al.* [1993]; Haynes *et al.* [2005]

No. 896

**MAb ID** F223

**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG3 $\lambda$ )  
**References** Cavacini *et al.* 1999

- F223: binds to HIV-1 gp120 and to uninfected lymphocytes binding to a 159-kd auto-antigen expressed on most B cells and a small fraction of T and NK cells – the antibody enhances HIV-1 infection in a complement-dependent manner – F223 light chains have a strong homology with VLgamma2, the heavy chain to the germline gene VH3-H.11 – N-linked carbohydrates are key for recognition of both gp120 and the autoantigen – MAb 3D6 also uses VH3 and has autoreactivity. Cavacini *et al.* [1999]

**No.** 897  
**MAb ID** F285  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1)  
**References** Wisniewski *et al.* 1996; Wisniewski *et al.* 1995

- F285: F285 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996]

**No.** 898  
**MAb ID** F2A3  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human  
**Ab Type** gp120 V3  
**Research Contact** James Robinson, Tulane University, New Orleans, LA, USA  
**References** Bowley *et al.* 2007; Liao *et al.* 2006; Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure, subtype comparisons, vaccine antigen design

- F2A3: Yeast display was compared to phage display and shown to select all the scFv identified by phage display and additional novel antibodies. F2A3 was used in competition assays to determine the binding region of the MAbs selected from the yeast displayed antibody library. Bowley *et al.* [2007]
- F2A3: The gp140 $\delta$ CFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. F2A3 was shown to bind specifically only to CON6 and subtype A gp140CFIs. No specific binding was

observed for the CON-S nor for the rest of the recombinant proteins and the two subtype B gp120 proteins. Liao *et al.* [2006] (**antibody binding site definition and exposure, vaccine antigen design, subtype comparisons**)

- F2A3: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. F2A3 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

**No.** 899  
**MAb ID** F3.9F  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**

**Species (Isotype)** human  
**Ab Type** gp120 V3  
**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- F3.9F: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. F3.9F has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

**No.** 900  
**MAb ID** F424  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Subtype** B

**Neutralizing**  
**Immunogen** HIV-1 infection

**Species (Isotype)** human  
**References** Ferrantelli *et al.* 2004a  
**Keywords** variant cross-recognition or cross-neutralization

- F424: Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. F424 is noted to be a MAb derived from a subtype B infected individual, that binds to an undefined epitope in gp120 and can neutralize some M group viruses, but it was not particularly effective at neutralization of the O group viruses tested. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)

**No.** 901  
**MAb ID** F425 B4e8 (F425-B4e8)  
**HXB2 Location** Env  
**Author Location** gp120 (V3)  
**Epitope**  
**Neutralizing**

**Immunogen  
Species (Isotype)**

**Ab Type** gp120 V3

**Research Contact** L. Cavacini

**References** Holl *et al.* 2006a; Pantophlet *et al.* 2007; Dhillon *et al.* 2007; Selvarajah *et al.* 2005; Pantophlet *et al.* 2004; Cavacini *et al.* 2003

**Keywords** antibody binding site definition and exposure, dendritic cells, neutralization, optimal epitope, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- F425 B4e8: Peptides containing the V3 epitope for F425 B4e8 did not inhibit neutralization by broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals. Dhillon *et al.* [2007] (**antibody binding site definition and exposure, neutralization**)
- F425 B4e8: The neutralization breadth of F425 B4e8 was assessed using a panel of 40 primary HIV-1 isolates. The Ab neutralized 8/16 clade B, 1/11 clade C and 2/6 clade D viruses, and its neutralization activity was comparable to mAb 447-52D. In contrast to previous reports, it is suggested here that F425 B4e8 interacts primarily with the crown/tip of V3, based on the scanning mutagenesis analyses of the V3 region, in particular with Ile309, Arg315, and Phe317. Pantophlet *et al.* [2007] (**antibody binding site definition and exposure, neutralization, optimal epitope, variant cross-recognition or cross-neutralization, subtype comparisons**)
- F425 B4e8: This Ab was shown to inhibit HIV-1 BaL replication in both macrophages and PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**dendritic cells**)
- F425 B4e8: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V3 MAbs (447-52D, 19b, F245-B4e8 and 39F) bound to the GDMR antigen, but either did not bind or had diminished binding to mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- F425 B4e8: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including F425 B4e8. This MAb bound to the initial

construct, but introduction of glycosylation sites at positions 320 and 325 inhibited binding. Pantophlet *et al.* [2004]

**No.** 902

**MAb ID** F425B4a1

**HXB2 Location** Env

**Author Location** gp120 (V3)

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** (IgG1λ)

**Ab Type** gp120 V3

**References** Holl *et al.* 2006a

**Keywords** dendritic cells, neutralization

- F425B4a1: This Ab was shown to inhibit HIV-1 BaL replication in macrophages but not in PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication occurs by an IgG-FcγR-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**neutralization, dendritic cells**)

**No.** 903

**MAb ID** F7

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* GM-CSF

**Species (Isotype)** mouse (IgG1)

**References** del Real *et al.* 1999

- F7: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – F7 was a gp120 specific MAb from a BALBc mouse and had VH gene 7183(81X), previously found expressed only in fetal liver. del Real *et al.* [1999]

**No.** 904

**MAb ID** Fab A12

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**References** Binley *et al.* 1996

- Fab A12: Uncharacterized epitope – variable regions sequenced. Binley *et al.* [1996]

**No.** 905

**MAb ID** Fab A2

**HXB2 Location** Env  
**Author Location** gp41 (LAI)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**References** Binley *et al.* 1996

- Fab A2: Uncharacterized epitope – variable regions sequenced. Binley *et al.* [1996]

**No.** 906  
**MAb ID** Fab L9  
**HXB2 Location** Env  
**Author Location** gp41 (LAI)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\kappa$ )  
**References** Binley *et al.* 1996

- Fab L9: Uncharacterized epitope – variable regions sequenced. Binley *et al.* [1996]

**No.** 907  
**MAb ID** G12  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120  
**Species (Isotype)** mouse (IgM)  
**References** del Real *et al.* 1999

- G12: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – G12 was a gp120 from a BALBc reconstructed nude mouse and had VH gene 7183-6. del Real *et al.* [1999]

**No.** 908  
**MAb ID** G2  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120  
**Species (Isotype)** mouse (IgM)  
**References** del Real *et al.* 1999

- G2: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – G2 was a gp120 from a BALBc reconstructed nude mouse and had VH gene Q52. del Real *et al.* [1999]

**No.** 909  
**MAb ID** H2  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human (IgM $\kappa$ )  
**Research Contact** BioInvent, Lund, Sweden, commercial  
**References** Muller *et al.* 1991

- H2: Anti-idiotypic MAbs (10B3 and 2A11) against MAb H2 were generated by immunization of BALBc mice with H2 – they also react with seropositive sera. Muller *et al.* [1991]

**No.** 910  
**MAb ID** H8  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* chimeric GM-CSF *Strain:* B clade IIIB *HIV component:* gp120  
**Species (Isotype)** mouse (IgM)  
**References** del Real *et al.* 1999

- H8: Murine antibody response to the chimeric construction granulocyte-macrophage colony stimulating factor GM-CSF/gp120 was tested, MAbs from normal mice were gp120 specific, MAbs from nude mice bound gp120 but were polyreactive, and from reconstituted mice were half way between – the anti-gp120 response used a high frequency of VH81X, VHQ52, and VH7183 genes, a family used during fetal life and associated with autoimmunity – H8 was a gp120 from a BALBc reconstructed nude mouse and had VH gene Q52. del Real *et al.* [1999]

**No.** 911  
**MAb ID** HBW4  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**References** Wisniewski *et al.* 1996; Wisniewski *et al.* 1995; Moran *et al.* 1993



- HBW4: HBW4 is V H2 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996]
- HBW4: Heavy (V HII) and light (V lambdaII) chain sequenced. Moran *et al.* [1993]

No. 912

MAB ID HIVIG

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing P

Immunogen HIV-1 infection

Species (Isotype) human

References Nichols *et al.* 2002

- NYBC-HIVIG derived from patients with high NAb titers and NABI-HIVIG derived from patients with high anti-p24 Ab titers were compared in neutralizing assay against a panel of six primary isolates – both could neutralize all isolates tested but the NYBC-HIVIG dose required for 50% neutralization was of 3.2 fold lower, showing source plasmas influence the effective concentration of NAb present in HIVIG. Nichols *et al.* [2002]

No. 913

MAB ID IVI-4G6

HXB2 Location Env

Author Location gp41

Epitope

Neutralizing

Immunogen vaccine

Species (Isotype) mouse (IgG2b)

Research Contact K. Miyakoshi (Feji-Rebio Co, Tokyo, Japan)

References Yin *et al.* 2001

- IVI-4G6: A bi-specific Ab (BFA) was made by combining Fab fragments of gp41-specific MAb IVI-4G6 and CD3-specific Mab UCHT1 – the BFA suppressed HIV-1 propagation culture and eliminated latently infected cells. Yin *et al.* [2001]

No. 914

MAB ID IgA6/30λ

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing yes

Immunogen HIV-1 exposed seronegative

Species (Isotype) human

References Berry *et al.* 2003

**Keywords** antibody generation, antibody sequence variable domain, genital and mucosal immunity, HIV exposed persistently seronegative (HEPS)

- A panel of anti-gp120 single-chain variable fragment (scFv) Ab was isolated from cervical B lymphocytes of unexposed uninfected Kenyan prostitutes. These Abs recognize gp120 in ELISA and using flow cytometry. IgG1b12 does not inhibit binding of the new clones to HIV, so the epitopes are distinct. Sequencing of the V genes of the scFv clones show they are unique. Berry *et al.* [2003] (**antibody generation,**

**genital and mucosal immunity, HIV exposed persistently seronegative (HEPS), antibody sequence variable domain)**

No. 915

MAB ID IgA6/5k

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing yes

Immunogen HIV-1 exposed seronegative

Species (Isotype) human

References Berry *et al.* 2003

**Keywords** antibody generation, antibody sequence variable domain, genital and mucosal immunity, HIV exposed persistently seronegative (HEPS)

- A panel of anti-gp120 single-chain variable fragment (scFv) Ab was isolated from cervical B lymphocytes of unexposed uninfected Kenyan prostitutes. These Abs recognize gp120 in ELISA and using flow cytometry. IgG1b12 does not inhibit binding of the new clones to HIV, so the epitopes are distinct. Sequencing of the V genes of the scFv clones show they are unique. Berry *et al.* [2003] (**antibody generation, genital and mucosal immunity, HIV exposed persistently seronegative (HEPS), antibody sequence variable domain)**

No. 916

MAB ID IgA6/L4

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing yes

Immunogen HIV-1 exposed seronegative

Species (Isotype) human

References Berry *et al.* 2003

**Keywords** antibody generation, antibody sequence variable domain, genital and mucosal immunity, HIV exposed persistently seronegative (HEPS)

- A panel of anti-gp120 single-chain variable fragment (scFv) Ab was isolated from cervical B lymphocytes of unexposed uninfected Kenyan prostitutes. These Abs recognize gp120 in ELISA and using flow cytometry. IgG1b12 does not inhibit binding of the new clones to HIV, so the epitopes are distinct. IgA6/4L is neutralizing. Sequencing of the V genes of the scFv clones show they are unique. Berry *et al.* [2003] (**antibody generation, genital and mucosal immunity, HIV exposed persistently seronegative (HEPS), antibody sequence variable domain)**

No. 917

MAB ID K14

HXB2 Location Env

Author Location gp41

Epitope

Neutralizing no

Immunogen

Species (Isotype) human (IgG1)

**References** Schutten *et al.* 1997; Schutten *et al.* 1996; Schutten *et al.* 1995b; Schutten *et al.* 1995a; Teeuwssen *et al.* 1990

- K14: In a study of NSI and SI virus neutralization, K14 did not influence viral entry. Schutten *et al.* [1997]
- K14: Reduced affinity for both SI and NSI viruses relative to MAb MN215, failed to neutralize SI strain. Schutten *et al.* [1995b]
- K14: Did not bind to peptides spanning gp41, but it does not react with Env deletion mutant 643-692 – does not react with HIV-2– competition experiments showed this was an immunodominant conserved epitope in HIV-1 positive sera from Europe and Africa. Teeuwssen *et al.* [1990]

No. 918

**MAb ID** KU32

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- KU32: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. KU32 was noted to have some polyspecific autoreactivity in the text, but it was not clear how this was manifested from the results. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 919

**MAb ID** LA15

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CCR5BS

**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- LA15: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. LA15 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 920

**MAb ID** LA21

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 V3

**References** Haynes *et al.* 2005

**Keywords** antibody binding site definition and exposure

- LA21: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. LA21 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

No. 921

**MAb ID** M2

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

**Species (Isotype)**

**Ab Type** gp120 V4

**References** Ren *et al.* 2005

**Keywords** antibody binding site definition and exposure, neutralization

- M2: This antibody is specific for a peptide flag inserted into the V4 loop of YU-2, a neutralization resistant variant with a short V4 loop. IgG1b12 and 2F5 could neutralize both the WT YU-2 and the modified variant. The high diversity of V4 suggests it does not play a direct role in receptor binding or viral entry, yet M2, specific for the peptide insert tag, can neutralize the modified virus, demonstrating that neutralizing activity doesn't have to block functionality of the virus. Ren *et al.* [2005] (**antibody binding site definition and exposure, neutralization**)

No. 922

**MAb ID** M25

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* purified HIV-1

**Species (Isotype)** mouse (IgGκ)

**References** Watkins *et al.* 1996; di Marzo Veronese *et al.* 1985

- M25: heavy and light chains cloned and sequenced – binding requires heavy and light chain in combination, in contrast to M77. Watkins *et al.* [1996]

No. 923

**MAb ID** MAG 6B

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* sCD4-gp120 complex *Strain:*  
B clade HXB2 *HIV component:* gp120

**Species (Isotype)** mouse

**Research Contact** C. Y. Kang, IDEC Inc

**References** Kang *et al.* 1994

- MAG 6B: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R or G or A, 262 N/T, 368 D/R or T, 370 E/R or Q, 381 E/P, 384 Y/E, 421 K/L, 475 M/S, 477 D/V. Kang *et al.* [1994]

**No.** 924

**MAb ID** MO28

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing** no

**Immunogen** *in vitro* stimulation or selection

**Species (Isotype)** human (IgM)

**References** Ohlin *et al.* 1989

- MO28: This antibody was raised by *in vitro* stimulation with a recombinant Env penv9 – the discontinuous epitope involves hydrophobic regions 632-646, 677-681 and 687-691, proximal to and spanning the transmembrane region – this specificity is unusual in HIV-1 positive sera. Ohlin *et al.* [1989]

**No.** 925

**MAb ID** MO30

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing** no

**Immunogen** *in vitro* stimulation or selection

**Species (Isotype)** human (IgM)

**References** Ohlin *et al.* 1989

- MO30: This antibody was raised by *in vitro* stimulation with a recombinant Env penv9 – the discontinuous epitope involves hydrophobic regions 632-646, 677-681 and 687-691, proximal to and spanning the transmembrane region – this specificity is unusual in HIV-1 positive sera. Ohlin *et al.* [1989]

**No.** 926

**MAb ID** MO43

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing** no

**Immunogen** *in vitro* stimulation or selection

**Species (Isotype)** human (IgM)

**References** Ohlin *et al.* 1989

- MO43: This antibody was raised by *in vitro* stimulation with a recombinant Env penv9 – the discontinuous epitope of MO43 involves hydrophobic regions 632-646, 677-681 and 687-691, proximal to and spanning the transmembrane region – this specificity is unusual in HIV-1 positive sera. Ohlin *et al.* [1989]

**No.** 927

**MAb ID** N2-4

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Research Contact** Evan Hersh and Yoh-Ichi Matsumoto

**References** Robinson *et al.* 1990b

- N2-4: NIH AIDS Research and Reference Reagent Program: 528.
- N2-4: No enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b]

**No.** 928

**MAb ID** N70-2.3a

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1)

**Research Contact** James Robinson, Tulane University, LA

**References** Takeda *et al.* 1992; Robinson *et al.* 1990a

- N70-2.3a: Fc receptor mediated enhancement of HIV-1 infection – binds a conformational site in the carboxyl half of gp120, distinct from 1.5e. Takeda *et al.* [1992]
- N70-2.3a: Broad reactivity. Robinson *et al.* [1990a]

**No.** 929

**MAb ID** P3C8

**HXB2 Location** Env

**Author Location** gp120 (SF162)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp140

**Species (Isotype)** mouse

**Ab Type** gp120 V1

**Research Contact** Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatatos@sbri.org

**References** Kraft *et al.* 2007

**Keywords** escape, neutralization

- P3C8: Viruses from early and late infection of a macaque with SHIV SF162P4 were resistant to contemporaneous serum that had broadly reactive NAbs. SF162 was highly susceptible to neutralization by anti-V3 MAbs 447D and P3E1, as well as anti-V1 MAb P3C8, while envelopes cloned from this animal at 304 days and at 643 days (time of death) post infection had developed resistance to all three of these antibodies. This is a new anti-V1 loop Ab isolated from mice immunized with SF162-derived gp140 proteins. Kraft *et al.* [2007] (**neutralization, escape**)

**No.** 930

**MAb ID** P3E1

**HXB2 Location** Env

**Author Location** gp41 (SF162)

**Epitope**

**Subtype** B

**Neutralizing****Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp140**Species (Isotype)** mouse**Ab Type** gp120 V3**Research Contact** Nina Derby or Leo Stamatatos, Seattle Biomedical Research Institute, Seattle, WA, USA, leo.stamatatos@sbri.org**References** Kraft *et al.* 2007**Keywords** escape, neutralization

- P3E1: Viruses from early and late infection of a macaque with SHIV SF162P4 were resistant to contemporaneous serum that had broadly reactive NABs. SF162 was highly susceptible to neutralization by anti-V3 MAbs 447D and P3E1, as well as anti-V1 MAb P3C8, while envelopes cloned from this animal at 304 days and at 643 days (time of death) post infection had developed resistance to all three of these antibodies. This is a new anti-V3 loop Ab isolated from mice immunized with SF162-derived gp140 proteins. Kraft *et al.* [2007] (**neutralization, escape**)

**No.** 931**MAb ID** P43110**HXB2 Location** Env**Author Location** gp120**Epitope****Neutralizing****Immunogen****Species (Isotype)****Research Contact** Advanced Biosciences (Kensington, MD)**References** VanCott *et al.* 1995; di Marzo Veronese *et al.* 1992

- P43110: Does not recognized denatured form of the gp120 protein. VanCott *et al.* [1995]

**No.** 932**MAb ID** P5-3**HXB2 Location** Env**Author Location** gp120**Epitope****Neutralizing****Immunogen** HIV-1 infection**Species (Isotype)** human (IgG1λ)**Research Contact** Evan Hersh and Yoh-Ichi Matsumoto**References** Pincus *et al.* 1991; Robinson *et al.* 1990b

- P5-3: NIH AIDS Research and Reference Reagent Program: 378.
- P5-3: Poor immunotoxin activity when coupled to RAC – isotype specified as: IgG3λ. Pincus *et al.* [1991]
- P5-3: No enhancing activity for HIV-1 IIIB. Robinson *et al.* [1990b]

**No.** 933**MAb ID** PA-1**HXB2 Location** Env**Author Location****Epitope****Neutralizing** No**Immunogen****Species (Isotype)****Ab Type** gp120 V3**Research Contact** Dr, William Olson, Progenics Pharmaceuticals**References** Dey *et al.* 2007**Keywords** vaccine antigen design

- PA-1: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP trimers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. 17b binding was induced similarly by CD4 for the WT and stabilized forms. Non-neutralizing MAbs PA-1 (V3) and b6 (CD4BS) bound less efficiently to the stabilized trimer. Dey *et al.* [2007] (**vaccine antigen design**)

**No.** 934**MAb ID** Sb1**HXB2 Location** Env**Author Location** gp120 (JR-FL)**Epitope****Subtype** B**Neutralizing** no**Immunogen** HIV-1 infection**Species (Isotype)** human (IgG)**Ab Type** gp120 CD4i**References** Bowley *et al.* 2007; Choe *et al.* 2003**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, assay standardization/improvement, binding affinity, co-receptor

- Sb1: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. Sb1 was identified using both methods, and is a CD4i antibody. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)
- Sb1: Sb1 was obtained from an HIV-1 infected individual with a potent and broadly neutralizing activity of his serum. It was shown that scFv Sb1 was sulfate-modified and it is implied that the sulfates are localized exclusively within the heavy chain CDR3 region of this MAb. Binding efficiency of scFv Sb1 to ADA gp120 was doubled in the presence of CD4, showing that this MAb is CD4-induced. Association of scFv Sb1 with ADA gp120-CD4-Ig complex was partially inhibited by a sulfated peptide with a sequence corresponding to

the CCR5 amino terminus, indicating that Sb1 binds a CD4-enhanced epitope overlapping the binding domain of CCR5 amino terminus. scFv Sb1 was shown to efficiently bind to gp120 of three R5 isolates but not to the HXBc2 X4 isolate. Choe *et al.* [2003] (**antibody binding site definition and exposure, co-receptor**)

**No.** 935  
**MAb ID** T15G1 (TG15)  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)**  
**References** Lee *et al.* 2006; Binley *et al.* 1999  
**Keywords** antibody binding site definition and exposure, dendritic cells, neutralization, subtype comparisons

- TG15: Unlike the nonneutralizing TG15 MAb, the membrane bound scFv derived from this MAb was shown to have broad neutralizing activity to subtype A, C and D HIV-1 primary isolates. In addition to inhibition of cell-free viruses, the cell surface expressed scFv significantly blocked transfer of captured HIV-1 from DCs to target CD4 T-cells. Lee *et al.* [2006] (**antibody binding site definition and exposure, neutralization, dendritic cells, subtype comparisons**)
- T15G1: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]

**No.** 936  
**MAb ID** T20  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140  
**Species (Isotype)** mouse (IgG)  
**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD  
**References** Sugiura *et al.* 1999; Otteken *et al.* 1996; Earl *et al.* 1994

- T20: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T20 is part of a group of MAbs labeled AII – all AII MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, and could only partially blocked CD4 binding. Sugiura *et al.* [1999]
- T20: Pulse label experiments of 4 MAbs (D20, D27, T20, and T22) binding to noncleavable gp140 revealed that these anti-CD4BS MAbs bound with a delay, and that the epitope formed with a t 1/2 of about 10 minutes. Otteken *et al.* [1996]
- T20: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 937  
**MAb ID** T27  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140  
**Species (Isotype)** mouse (IgG)  
**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

- References** Sugiura *et al.* 1999; Earl *et al.* 1994
- T27: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T27 is part of a group of MAbs labeled AII – all AII MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, and could only partially blocked CD4 binding. Sugiura *et al.* [1999]
  - T27: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 938  
**MAb ID** T3  
**HXB2 Location** Env  
**Author Location** gp41 (HXB2)  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* tetrameric Env *HIV component:* Env  
**Species (Isotype)** mouse (IgG)  
**References** Yang *et al.* 2000; Zwick *et al.* 2001b; Earl *et al.* 1997; Earl *et al.* 1994

- T3: T3 partially competes with MAb Z13, but not MAb 4E10, both of which bind to gp41 proximally to the 2F5 epitope and have a broad neutralizing potential. Zwick *et al.* [2001b]
- T3: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – gp41 MAbs T4, D12, T3, and D50 bound less efficiently to gp140-GNC4 than did pooled sera, but T4 and D12 recognized the gp140-GNC4 timer equivalently to gp140(-), and T3 and D50 recognized the trimer at greater levels than gp140(-). Yang *et al.* [2000]

- T3: Partially conformation dependent – doesn't bind to short peptides, but does bind to the region spanning 641-683 – binding can be blocked by MAbs D43, D38 and D45 – MAbs in this competition group reacted with 9/10 HIV-1 strains, not binding to JRFL. Earl *et al.* [1997]
- T3: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 939

MAB ID T30

HXB2 Location Env

Author Location gp41 (580–640)

Epitope

Neutralizing no

Immunogen vaccine

Vector/Type: tetrameric Env HIV component: Env

Species (Isotype) mouse

Research Contact C. Broder

References Billington *et al.* 2007; Ohagen *et al.* 2003; Earl *et al.* 1997; Earl *et al.* 1994

Keywords antibody binding site definition and exposure, antibody generation, brain/CSF, escape

- T30: Binds to ILAVERY...NNYTS, and binding involves the N-linked carbohydrate at N616. The T30 antibody was used to partially purify a D subtype rgp140 that forms a stable trimer and may be suitable for structural studies. The partially purified protein was used to immunize mice, and one of the MAbs, 2E2, was used to then further purify the protein. Billington *et al.* [2007]
- T30: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. T30 recognized most variants (10/13) gp41 by WB, and all of the gp160s. Ohagen *et al.* [2003] (**brain/CSF, escape**)
- T30: Binds in the region 580 to 640, but does not bind to peptides spanning this region – binding depends on N-linked glycosylation of Asn 616 – no other antibody tested inhibited binding, but binding could be inhibited by sera from HIV+ individuals. Earl *et al.* [1997] (**antibody binding site definition and exposure**)
- T30: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 940

MAB ID T4

HXB2 Location Env

Author Location gp41 (IIIB)

Epitope

Neutralizing L

Immunogen vaccine

Vector/Type: vaccinia Strain: B clade IIIB HIV component: oligomeric gp140

Species (Isotype) mouse (IgG)

**References** Srivastava *et al.* 2002; Yang *et al.* 2000; Stamatatos *et al.* 2000; Binley *et al.* 1999; Earl *et al.* 1997; Otteken *et al.* 1996; Weissenhorn *et al.* 1996; Richardson *et al.* 1996; Broder *et al.* 1994; Earl *et al.* 1994

**Keywords** antibody binding site definition and exposure, antibody generation, antibody interactions, vaccine antigen design

- T4: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – T4 recognized o-gp140. Srivastava *et al.* [2002] (**antibody binding site definition and exposure**)
- T4: Soluble gp140 derived from SF162, a neutralization-resistant primary isolate, and SF162AV2 a neutralization-susceptible isolate with 30 amino acids deleted from the V2 loop, were generated with or without the gp120-gp41 cleavage site intact – all forms are recognized by oligomer-specific MAb T4 and show enhanced binding of CD4i MAb 17b when sCD4 is bound – the fused forms are less efficiently recognized than the cleaved forms by polyclonal neutralizing sera from HIV-infected patients – the V3 loop is more exposed on the fused form. Stamatatos *et al.* [2000] (**vaccine antigen design**)
- T4: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – gp41 MAbs T4, D12, T3, and D50 bound less efficiently to gp140-GNC4 than did pooled sera, but T4 and D12 recognized the gp140-GNC4 trimer equivalently to gp140(-), and T3 and D50 recognized the trimer at greater levels than gp140(-). Yang *et al.* [2000] (**vaccine antigen design**)
- T4: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**vaccine antigen design**)
- T4: This antibody, along with 7 others (M10, D41, D54, T6, T9, T10 and T35), can block the linear murine MAb D61, and the human MAb 246-D, which both bind to the immunodominant region near the two Cys in gp41 – most of these antibodies are oligomer dependent – all of the MAbs are reactive with ten different HIV-1 strains – members of this competi-

tion group are blocked by sera from HIV-1 + individuals. Earl *et al.* [1997] (**antibody interactions**)

- T4: MAbs T4 and T6 bind only to oligomer, and pulse chase experiments indicate that the epitope is very slow to form, requiring one to two hours. Otteken *et al.* [1996] (**antibody binding site definition and exposure**)
- T4: Does not bind to soluble monomeric gp41(21-166) that lacks the fusion peptide and membrane anchor, only to the oligomer gp140, as does T6. Weissenhorn *et al.* [1996] (**antibody binding site definition and exposure**)
- T4: one of five MAbs (T4, T6, T9, T10 and T35) in a competition group that bind to a conformation-dependent epitope in gp41 and is oligomer specific – neutralizes IIIB and SF2. Broder *et al.* [1994] (**antibody binding site definition and exposure**)
- T4: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 941

**MAb ID** m14

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Neutralizing P**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**Research Contact** D. S. Dimitrov

**References** Choudhry *et al.* 2007

**Keywords** antibody generation, antibody sequence variable domain, neutralization

- m14: m18 and m14 have sequences and binding activity similar to two other broadly neutralizing MAbs, m22 and m24, that were identified by screening a phage-displayed antibody library with a gp140 from the donor R2, who had high levels of broadly neutralizing antibodies. All 4 MAbs competed with IgG1b12 and sCD4. Choudhry *et al.* [2007] (**antibody generation, neutralization, antibody sequence variable domain**)

No. 942

**MAb ID** m16 (scFv m16)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing P**

**Immunogen** in vitro stimulation or selection

**Species (Isotype)** human

**Ab Type** gp120 CD4i

**References** Choudhry *et al.* 2006; Zhang *et al.* 2004b

**Keywords** autologous responses, co-receptor, enhancing activity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- m16: Neutralization of HIV-1 primary isolates of clade B by different formats of m16 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory

concentration of m16 in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor, neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)

- m16: This antibody was selected by sequential antigen panning (SAP) of a human phage display library against recombinant soluble HIV-1 envelope glycoproteins (Envs) (gp140s) and their complexes with soluble CD4. m16 inhibited cell fusion mediated by the Envs of 9 HIV-1 isolates from clades A, B, E and G with potency comparable to that Fab X5. Zhang *et al.* [2004b] (**autologous responses, enhancing activity, neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 943

**MAb ID** m18 (M18, Fab M18)

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Neutralizing P**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**Research Contact** D. S. Dimitrov

**References** Choudhry *et al.* 2007; McCaffrey *et al.* 2004; Zhang *et al.* 2003

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- m18: m18 and m14 have sequences and binding activity similar to two other broadly neutralizing MAbs, m22 and m24, that were identified by screening a phage-displayed antibody library with a gp140 from the donor R2, who had high levels of broadly neutralizing antibodies. All 4 MAbs competed with IgG1b12 and sCD4. Choudhry *et al.* [2007] (**antibody generation, neutralization, antibody sequence variable domain**)
- m18: Called M18. Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) or adjacent to V3 in C2 (GM292 C2), left SF162 susceptible to neutralization by Fab M18, and the glycan mutants in C3 (GM329 C3), C4 (GM438 C4), or V5 (GM454 V5) became resistant to M18 neutralization. The M18 epitope is unknown. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure, vaccine antigen design**)
- m18: m18 was selected from a human Fab phage display library by a new method called sequential antigen panning (SAP), using a series of antigens to screen the library to pick broadly cross-reactive isolates. The epitope of m18 is independent of CD4 binding. The phage display library was constructed using the combined bone marrow of three long term non-progressors with potent NAb activity in their sera. m18

bound to gp140s from primary isolates from clades A-F with nM affinities. The ability to block cell mediated fusion by m18 was compared to Fabs X5 and b12 for a clade A, CRF01 EA, G, and 6 clade B isolates, and the inhibitory activity of m18 was slightly lower but comparable to neutralizing Fabs b12 and X5. It also showed broad cross-neutralization; 11/15 pseudotyped Envs from primary isolates from clades A-F were inhibited in an IC50 assay at concentration less than or equal to 100 ug/ml; X5 was also tested and somewhat more potent, generally requiring lower concentrations and inhibiting 13/15 primary isolates. Zhang *et al.* [2003] (**antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 944

MAb ID m22

HXB2 Location Env

Author Location Env

Epitope

Neutralizing P

Immunogen HIV-1 infection

Species (Isotype) human

Ab Type gp120 CD4BS

Research Contact D. S. Dimitrov

References Choudhry *et al.* 2007

Keywords antibody generation, antibody sequence variable domain, neutralization

- m22: m18 and m14 have sequences and binding activity similar to two other broadly neutralizing MAbs, m22 and m24, that were identified by screening a phage-displayed antibody library with a gp140 from the donor R2, who had high levels of broadly neutralizing antibodies. All 4 MAbs competed with IgG1b12 and sCD4. Choudhry *et al.* [2007] (**antibody generation, neutralization, antibody sequence variable domain**)

No. 945

MAb ID m24

HXB2 Location Env

Author Location Env

Epitope

Neutralizing P

Immunogen HIV-1 infection

Species (Isotype) human

Ab Type gp120 CD4BS

Research Contact D. S. Dimitrov

References Choudhry *et al.* 2007

Keywords antibody generation, antibody sequence variable domain, neutralization

- m24: m18 and m14 have sequences and binding activity similar to two other broadly neutralizing MAbs, m22 and m24, that were identified by screening a phage-displayed antibody library with a gp140 from the donor R2, who had high levels of broadly neutralizing antibodies. All 4 MAbs competed with IgG1b12 and sCD4. Choudhry *et al.* [2007] (**antibody generation, neutralization, antibody sequence variable domain**)

No. 946

MAb ID m46

HXB2 Location Env

Author Location gp41

Epitope

Neutralizing P

Immunogen HIV-1 infection

Species (Isotype) human

Research Contact D. S. Dimitrov

References Choudhry *et al.* 2007

Keywords antibody generation, antibody sequence variable domain, assay standardization/improvement, neutralization, subtype comparisons

- m46: m46 was identified by screening a phage-displayed antibody library with a gp140 from the donor R2, who had high levels of broadly neutralizing antibodies. m46 binds to a conformational epitope on gp41 and did not compete with 2F5, 4E10 or Z13. It bound to a 5 helix bundle, but not to N-heptad repeat coil-coils or a 6-helix bundle. It is broadly neutralizing, to levels comparable to T20, when tested using PBMC with low CCR5 levels, but less potently when the neutralization assay was performed in a cell line with high CCR5 levels. Isolates from different clades had differing degrees of neutralization sensitivity. Choudhry *et al.* [2007] (**antibody generation, neutralization, subtype comparisons, antibody sequence variable domain, assay standardization/improvement**)

No. 947

MAb ID m9 (scFv m9)

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing P

Immunogen in vitro stimulation or selection

Species (Isotype) human (IgG)

Ab Type gp120 adjacent to CD4BS

Research Contact Zhang2004

References Choudhry *et al.* 2006; Zhang *et al.* 2004a

Keywords antibody generation, co-receptor, enhancing activity, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- m9: Neutralization of HIV-1 primary isolates from different clades (A, B, C, D and E) by m9 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of m9 in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor, neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- m9: This antibody was selected by subjecting a random mutagenesis library of the scFv X5 to sequential rounds of selection on non-homologous HIV-1 envelope glycoproteins dubbed sequential antigen panning (SAP). scFv m9 has higher neutralization activity and is able to inhibit a broader range of HIV-1 primary isolates compared to scFv X5. Zhang *et al.* [2004a] (**antibody generation, enhancing activity, neutralization**)

No. 948

MAb ID multiple Fabs

HXB2 Location Env



**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Burton *et al.* 1991

- A panel of anti-gp120 Fabs was generated by antigen selection from a random combinatorial library prepared from bone marrow from an asymptomatic individual. Burton *et al.* [1991]

**No.** 949

**MAb ID** multiple MAbs

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* gp120

**Species (Isotype)** mouse

**References** Denisova *et al.* 1996

- When gp120 was used as an immunogen, in contrast to gp120 bound to an anti-V3 MAb, few MAbs were generated and all bound better to the native than to the denatured protein – MAbs generated were: G1B12, G2F7, G9G8, G12F12, G1B8, G11F11, G9E8, G1B11, G1B6, G6F2, G2E7. Denisova *et al.* [1996]

**No.** 950

**MAb ID** multiple MAbs

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* gp120-CD4 complex *HIV component:* gp120

**Species (Isotype)** mouse

**References** Denisova *et al.* 1996

- When gp120-CD4 was used as an immunogen, in contrast to gp120 bound to an anti-V3 MAb, few MAbs were generated and all bound better to the native than to the denatured protein – MAbs generated were: CG43, CG41, CG49, CG53, CG42, CG4, CG46, CG40, CG52, CG51, CG48, CG50, CG125, CG124, CG121. Denisova *et al.* [1996]

**No.** 951

**MAb ID** multiple MAbs

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein-Ab complex *HIV component:* gp120-Mab complex

**Species (Isotype)** mouse

**References** Denisova *et al.* 1996

- When anti-V3 MAb M77 was bound to gp120 and used as an immunogen, it stimulated many MAbs to linear epitopes, as well as an array of MAbs to discontinuous epitope – 10 of 36 MAbs were mapped to linear epitopes and are mentioned elsewhere in this database, the others are: GV5H1, GV4D5, GV4G10, GV1A8, GV10H5, GV8E11, GV2H4, GV6E6, GV1F7, GV1G9, GV4G5, GV6B12, GV1E8, GV2B7, GV1B11, GV6H5, GV6G2, GV6B5, GV1E10, GV5E3, GV5B9, GV5F4, GV6G4, GV1A12, GV5C11, GV6B6, GV3C10. Denisova *et al.* [1996]

**No.** 952

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Neutralizing** L P

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG3)

**References** Scharf *et al.* 2001

- IgG3: HIVIG was separated into immunoglobulin classes and IgG3 neutralization of HIV strains X4, R5 and X4R5 strains was superior to IgG1 and IgG2, and IgG3 was also a more potent inhibitor of viral fusion – the IgG3 advantage was lost when only Fabs were considered, indicating the IgG3 neutralization efficacy is enhanced due to a longer hinge region of the heavy chain in comparison to IgG1 and IgG2. Scharf *et al.* [2001]

**No.** 953

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp140 (IIIB)

**Epitope**

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB *HIV component:* gp120, gp140 *Adjuvant:* MPL-SE adjuvant, QS21

**Species (Isotype)** rabbit (IgG)

**References** Earl *et al.* 2001

- Immunization of rabbits with oligomeric gp140 induced production of higher levels of cross-reactive neutralizing Abs than immunization with gp120 – immunization of Rhesus macaques with gp140 yielded strong NAb against IIIB, modest against other lab-adapted strains, and no NAb activity against primary isolates – most neutralizing activity could not be blocked by a V3 peptide – 3/4 vaccinated macaques showed no viral replication upon intravenous challenge with SHIV-HXB2. Earl *et al.* [2001]

**No.** 954

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp160 (IIIB)

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* gp160 *Adjuvant:* aluminum hydroxide

**Species (Isotype)** human

**References** Cox *et al.* 1999

- 60 asymptomatic HIV-1 infected patients were vaccinated with rec gp160 in alum, produced in a baculovirus expression vector in insect cells (VaxSyn), 64 received placebo, and all were followed in a 5 year longitudinal study – a mean of 78% of vaccinated and 82% of those receiving placebo had demonstrable ADCC at the different time intervals in the study, and the vaccine did not enhance ADCC production – patients with rapid and slow disease progression showed similar ADCC levels. Cox *et al.* [1999]

**No.** 955

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp160 (89.6)

**Epitope**

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* modified vaccinia Ankara (MVA) *Strain:* B clade 89.6 *HIV component:* Env, Gag-Pol *Adjuvant:* IL-2/Ig

**Species (Isotype)** macaque

**References** Barouch *et al.* 2001b

- Four rhesus macaques were vaccinated with a modified vaccinia Ankara (MVA) vaccine that elicited strong CTL responses as well as antibody responses. The animals were infected when challenged with pathogenic SHIV-89.6P, but had potent CTL responses, secondary NAb responses upon challenge, partial preservation of CD4+ T-cell counts, lower viral loads, and no evidence of disease or mortality by day 168 after challenge—monkeys that got a sham vaccine had high viral load, progressed to disease, and 2/4 were dead by day 168. Barouch *et al.* [2001b]

**No.** 956

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp160

**Epitope**

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Ahmad *et al.* 2001

- High CD4+ T-cell count and low viral load was correlated with high ADCC anti-HIV-1 Env Ab titers in a study of 46 HIV-1 infected individuals from all disease stages. Ahmad *et al.* [2001]

**No.** 957

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp160

**Epitope**

**Neutralizing** P

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**References** Beirnaert *et al.* 2001

- Neutralizing antibodies are thought to inhibit HIV entry by blocking either binding or fusion – six broadly cross-neutralizing sera that can neutralize group M and O viruses inhibit the binding to PBMCs – the nine primary isolates tested in this study represented very diverse subtypes and recombinant forms, and different co-receptor usage. Beirnaert *et al.* [2001]

**No.** 958

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp160

**Epitope**

**Neutralizing** P

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**References** Beirnaert *et al.* 2000

- Sera from 66 HIV individuals from diverse geographic locations could neutralize primary isolates to different extents: broad cross-neutralizing isolates could neutralize 14 primary isolates from HIV-1 group M clades A-H and three O isolates, limited cross-neutralizing sera neutralized some isolates, and non-neutralizing sera—6/7 broadly neutralizing sera were from African women, despite only 14/66 study subjects being women—ability to neutralize three key isolates, MN lab (envB/gagB, X4 coreceptor), VI525 (envG/gagH, envA/gagA, R5X4) and CA9 (Group O, R5) was predictive of being able to neutralize an additional set of 14 primary isolates. Beirnaert *et al.* [2000]

**No.** 959

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (SF2)

**Epitope**

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF2  
*HIV component:* gp120 *Adjuvant:* MF59, PLG

**Species (Isotype)** mouse, baboon

**References** O'Hagan *et al.* 2000

- Microparticles were used as an adjuvant for entrapped HIV-1 gp120 and induced strong serum IgG responses in mice – polylactide co-glycolide polymer (PLG) microparticles in combination with MF-59 had the highest response. O'Hagan *et al.* [2000]

**No.** 960

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (SF2, US4)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* DNA, protein *Strain:* B clade SF2, B clade US4 *HIV component:* gp120  
*Adjuvant:* aluminum phosphate, MF59, PLG

**Species (Isotype)** macaque, guinea pig, mouse

**References** O'Hagan *et al.* 2001

- DNA vaccines of codon-optimized Env and Gag genes driven by CMV promoters and absorbed on to PLG microparticles were more effective than naked DNA at eliciting strong Ab responses (more rapid, higher titer, more stable), comparable to gp120 in MF-59. O'Hagan *et al.* [2001]

No. 961

**MAb ID** polyclonal**HXB2 Location** Env**Author Location** gp120**Epitope****Neutralizing** L**Immunogen** HIV-1 infection**Species (Isotype)** chimpanzee (IgG)**References** Moore & Burton 1999; Shibata *et al.* 1999

- polyclonal: Commentary discussing this finding noting the particularly high neutralization titer and limited breadth of the chimpanzee sera used in this study. Moore & Burton [1999]
- polyclonal: Purified IgG from chimpanzee sera infected with several HIV-1 strains was used for passive administration to macaques which were subsequently challenged with the virulent SHIV bearing the HIV-1 env DH12 – *in vitro* neutralization correlated with protection *in vivo*. Shibata *et al.* [1999]

No. 962

**MAb ID** polyclonal**HXB2 Location** Env**Author Location** gp160 (MN)**Epitope****Neutralizing** L P**Immunogen** HIV-1 infection**Species (Isotype)** human (IgA)**References** Moja *et al.* 2000

- 15 samples isolated from parotid saliva were selected for study as they had anti-Env IgA – IgA neutralizing activity was detected that was not directed at either EDELKWA or the V3 loop. Moja *et al.* [2000]

No. 963

**MAb ID** polyclonal**HXB2 Location** Env**Author Location** gp120**Epitope****Neutralizing** L**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade MN, B clade SF2 *HIV component:* gp120**Species (Isotype)****References** McElrath *et al.* 2000

- After 3 immunizations, 210/241 (87%) HIV-1 uninfected vaccinees in a phase II trial developed NAb – of 140 patients receiving 4 vaccinations, 53% had persistent neutralizing antibodies to homologous virus, and 34% to heterologous virus, measured at day 728 after initial immunization – immunogens were well tolerated – but IVDUs had a decreased Ab response relative to lower risk groups. McElrath *et al.* [2000]

No. 964

**MAb ID** polyclonal**HXB2 Location** Env**Author Location** gp120**Epitope****Neutralizing****Immunogen** vaccine*Vector/Type:* vaccinia *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* GM-CSF/gp120 chimera**Species (Isotype)** mouse**References** Rodríguez *et al.* 1999

- The murine Ab response to a chimeric of granulocyte-macrophage colony stimulating factor GM-CSF/gp120 in vaccinia was not higher titer than the response to a gp120-vaccinia construct, but the breadth of the Ab response was greater – a cellular response of greater intensity was triggered to the GM-CSF/gp120 vaccinia construct, as measured by proliferation and Elispot. Rodríguez *et al.* [1999]

No. 965

**MAb ID** polyclonal**HXB2 Location** Env**Author Location** gp120 (YU2)**Epitope****Neutralizing****Immunogen** vaccine*Vector/Type:* stabilized Env trimer *Strain:* B clade HXBc2, B clade YU2 *HIV component:* Env**Species (Isotype)** mouse (IgG)**Research Contact** Joseph Sodroski, Harvard Medical School**References** Yang *et al.* 2001

- Soluble Env trimers were created that were designed to mimic functional Env oligomers – stabilized trimers could induce neutralizing antibodies more effectively than gp120, and Abs to the YU2 trimer were cross-reactive within clade B and could neutralize several primary and TCLA reactive strains – the stabilized primers did not neutralize primary isolates outside the B clade, from clades C, D, and E – HXBc2 stabilized trimer antigen elicited strong neutralizing Abs against the homologous isolate HXBc2 TCLA strain, but not against primary isolates. Yang *et al.* [2001]

No. 966

**MAb ID** polyclonal**HXB2 Location** Env**Author Location** gp120 (MN)**Epitope****Neutralizing****Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade MN *HIV component:* gp120 *Adjuvant:* aluminum hydroxide, QS21**Species (Isotype)** human**References** Evans *et al.* 2001

- Vaccination with QS21 adjuvant and rsgp120 elicited stronger and more sustained neutralizing antibody responses and lymphocyte proliferation with lower doses of rsgp120 than alum formulations, suggesting QS21 may be a means to reduce the dose of soluble protein. Evans *et al.* [2001]

**No.** 967  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** yes  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Binley *et al.* 2000

- HAART inhibited the development of anti-gp120 Ab when initiated during primary infection and sometimes in patients treated within 2 years of HIV-1 infection – HAART during primary infection usually did not inhibit the development of weak NAb responses against autologous virus – 3/4 patients intermittently adherent developed high titers of autologous NABs, largely coincident with brief viremic periods. Binley *et al.* [2000]

**No.** 968  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (SIV)  
**Epitope**  
**Neutralizing** yes  
**Immunogen** HIV-1 infection  
**Species (Isotype)** macaque  
**References** Reitter *et al.* 1998

- This study concerned an SIV mutated strain that lacked 4th, 5th and 6th sites for N-linked glycosylation – monkeys infected with the mutant viruses had increased neutralizing activity in their sera relative to monkeys infected with the parental strain. Reitter *et al.* [1998]

**No.** 969  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing** yes  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Kim *et al.* 2001

- After HAART reduction of viral load to <400 for three visits over a 12 month interval, 2/11 patients were found to have increased anti-Env Ab binding titers, and neutralizing Abs titers increased against primary isolates US1, and CM237 – no NAB titer increase was seen to more readily neutralized isolate BZ167 – this suggests that in certain individuals the control of HIV-1 by HAART may augment immune control of HIV. Kim *et al.* [2001]

**No.** 970  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing** yes  
**Immunogen** HIV-1 exposed seronegative  
**Species (Isotype)** human (IgA)  
**References** Kaul *et al.* 2001b

- Kaul *et al.* provide a concise summary of the findings concerning the presence of Mucosal IgA in highly exposed, uninfected subjects, arguing for a role in protection. Kaul *et al.* [2001b]

**No.** 971  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF2  
*HIV component:* gp120 *Adjuvant:* MF59  
**Species (Isotype)** human  
**References** Nitayaphan *et al.* 2000

- A phase I/II trial was conducted in 52 seronegative Thais immunizing with rgp120 SF2 – the vaccine was safe and 39/40 developed NAb responses to the autologous SF2, while 22/40 were able to cross-neutralize the heterologous strain MN. Nitayaphan *et al.* [2000]

**No.** 972  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (SF2)  
**Epitope**  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF2  
*HIV component:* gp120, p24 Gag *Adjuvant:* Immune stimulating complexes (ISCOM)

- Species (Isotype)** macaque  
**References** Heeney *et al.* 1998a
- The immune responses induced in Rhesus monkeys using two different immunization strategies was studied – one vaccine group was completely protected from challenge infection, the other vaccinees and controls became infected – protected animals had high titers of heterologous NABs, and HIV-1-specific T helper responses – increases in RANTES, MIP 1 alpha and MIP 1 beta produced by circulating CD8+ T cells were also associated with protection. Heeney *et al.* [1998a]

**No.** 973  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide, protein *Strain:* B clade SF2, B clade SF33 *HIV component:* gp120 *Adjuvant:* Immune stimulating complexes (ISCOM), MF59  
**Species (Isotype)** macaque  
**References** Verschoor *et al.* 1999

- Attempts were made to broaden immune responses induced in Rhesus monkeys by immunization of animals previously immunized that had resisted homologous challenge, with a second immunization with ISCOM-peptides or a boost with gp120 from SF33 – animals didn't survive a second challenge heterologous challenge virus SHIV(SF33) raising concerns about early antigenic sin. Verschoor *et al.* [1999]

**No.** 974

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF2, CRF01 CM235 *HIV component:* gp120  
*Adjuvant:* MF59

**Species (Isotype)** baboon

**References** VanCott *et al.* 1999

- Immunization with rgp120 CM235 (CRF01) induced Abs capable of neutralizing TCLA subtype E (CRF01) and subtype B isolates, while rgp120SF2 induced Abs could only neutralize subtype B TCLA isolates – neither immunogen induced Abs capable of neutralizing primary HIV-1 isolates – both rgp120CM235 and rgp120SF2 induced Abs to regions within C1, V1/V2, V3, and C5, but unique responses were induced by rgp120CM235 to epitopes within C2, and by rgp120SF2 to multiple epitopes within C3, V4, and C4 – CM235 baboon sera bound 3- to 12-fold more strongly than the SF2 baboon sera to all subtype E gp120s while binding to subtype B gp120s (except SF2) were within two to threefold for the SF2 and CM235 baboon sera. VanCott *et al.* [1999]

**No.** 975

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp140 (SF162DeltaV2)

**Epitope**

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor  
*Strain:* B clade SF162 *HIV component:* gp140  
*Adjuvant:* MF59

**Species (Isotype)** macaque, rabbit (IgG)

**References** Barnett *et al.* 2001

- SF162ΔV2 is a virus that has a 30 amino acids deletion in the V2 loop that does not abrogate its infectivity but renders it highly susceptible to neutralization—when incorporated into a codon-optimized DNA vaccine with a CMV promoter and delivered by gene gun, SF162ΔV2 gave higher neutralizing Ab titers against SF162 than did SF162 itself, and Abs that cross-neutralized non-homologous primary isolates were obtained only when SF162ΔV2, but not intact SF162, was used as the immunogen—Control MAbs 2F5 and 2G12 could neutralize all of the following primary isolates: 91US056(R5), 92US714(R5), 92US660(R5), 92HT593(R5X4), and BZ167(R5X4), while after the first protein boost, the sera from two SF162ΔV2 immunized macaques could neutralize 91US056(R5), 92US714(R5), 92US660(R5)

and ADA(R5), but not 92HT593(R5X4) or 92US657(R5)—the pattern of cross-recognition shifted after the second boost. Barnett *et al.* [2001]

**No.** 976

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**References** Binley *et al.* 1997b

- Retention of anti-Env antibodies and loss of anti-Gag antibodies during progression was studied, and suggested to be the result of the loss of T-cell help and the unique ability of Env to stimulate B cells even in a backdrop of declining CD4 cells, because of the ability of Env to bind to the CD4 molecule. Binley *et al.* [1997b]

**No.** 977

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (W61D)

**Epitope**

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade W61D *HIV component:* gp120

**Species (Isotype)** human

**References** Beddows *et al.* 1999

- rgp120 derived from a R5X4 subtype B virus, HIV-1 W61D, was used to vaccinate healthy volunteers and the resulting sera were compared with HIV-1 positive subjects – vaccinee sera had more potent responses to linear V1/V2 and V3 epitopes than did the sera from HIV-1 + individuals, but could only neutralize homologous or heterologous virus only after adaptation to T-cell lines – neutralization activity was lost after re-adaptation to growth in PBMCs – in contrast, sera from infected individuals could neutralize both PBMC and T-cell line adapted viruses. Beddows *et al.* [1999]

**No.** 978

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP) *HIV component:* Gag, gp120, V3

**Species (Isotype)** macaque

**References** Wagner *et al.* 1998b

- A VLP is a non-infectious virus-like particle self-assembled from HIV Pr55 gag – macaques were immunized with VLPs bound to either gp120 or V3+CD4 linear domains – Gag and Env specific CTL were stimulated in each case, and Ab response to gag and gp120 and was elicited, but the gp120 neutralizing response occurred only with whole gp120, not V3+CD4 – despite the CTL and Ab response, immunized

macaques were infected by intervenous challenge with SHIV chimeric challenge stock. Wagner *et al.* [1998b]

**No.** 979  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* gp120, gp160  
**Species (Isotype)** mouse  
**References** Shiver *et al.* 1997  
 • DNA vaccinations of BALBc mice with a gp120 or gp160 DNA vaccine elicited a strong T cell proliferative response with Th1-like secretion of gamma interferon and IL-2, with little or no IL-4, as well as antigen specific gp120 Abs. Shiver *et al.* [1997]

**No.** 980  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* DNA *HIV component:* Env, Gag, Pol, Vif *Adjuvant:* B7, IL-12  
**Species (Isotype)** mouse  
**References** Kim *et al.* 1997b  
 • A gag/pol, vif or CMN160 DNA vaccine, when delivered in conjunction with the plasmid encoding the co-stimulatory molecules B7 and IL-12, gave a dramatic increase in both the cytotoxic and proliferative responses in mice – the Ab response was detected by ELISA, but the CMN160 DNA vaccinated mice showed a neutralizing Ab response. Kim *et al.* [1997b]

**No.** 981  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Bradney *et al.* 1999  
 • Sera were taken from long term non-progressors and evidence for viral escape was noted – serum could neutralize earlier autologous isolates, but not contemporary isolates. Bradney *et al.* [1999]

**No.** 982  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L P  
**Immunogen** vaccine

*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade SF2 *HIV component:* Env, Gag

**Species (Isotype)** human  
**References** Belshe *et al.* 1998  
 • NAbs were obtained by a HIV-1 gag/env in canary pox vaccination of eight volunteers after boosting with rgp120 against lab strains – 1/8 primary isolates was neutralized, BZ167. Belshe *et al.* [1998]

**No.** 983  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, Protease *Adjuvant:* MF59  
**Species (Isotype)** human  
**References** Belshe *et al.* 2001; Belshe *et al.* 1998  
 • A phase 2 trial was conducted in 435 volunteers with vCP201, a canary pox vector carrying gp120 (MN in vCP201, and SF2 in the boost), p55 (LAI) and protease (LAI), either alone or with a gp120 boost – NAbs against MN were obtained in 56% of those who received vCP201 alone, and in 94% of those who got the prime with the gp120 boost. Belshe *et al.* [1998]

**No.** 984  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human  
**References** Neshat *et al.* 2000  
 • HIV-1 gp120 appears to be a B cell superantigen that binds to members of the V<sub>H3</sub> Ig gene family—the gp120 binding site was localized to the Fab portion of the Ab, and discontinuous residues in the V<sub>H</sub> region were critical. Neshat *et al.* [2000]

**No.** 985  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp41 (539–684 BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp41  
**Species (Isotype)** mouse (IgG)  
**References** Bai *et al.* 2000  
 • Murine rsgp41 antisera recognized a common epitope on human IFN $\alpha$  (aa 29-35 and aa 123-140) and on human IFN $\beta$  (aa 31-37 and aa 125-142), suggesting that elevated levels of Ab to IFNs found in HIV+ individuals may be due to a cross-reactive gp41 response. Bai *et al.* [2000]

**No.** 986  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade 89.6, B clade ADA, B clade IIIB *HIV component:* gp120 *Adjuvant:* C3d fusion  
**Species (Isotype)** mouse (IgG)  
**References** Ross *et al.* 2001

- gp120 was fused with murine complement protein C3d in a DNA vaccine to enhance the titers of Ab to Env – fusion to C3d resulted in a more rapid onset of Ab response and avidity maturation, after three immunizations in BALB/c mice with DNA on a gold bead delivered with a gene gun, but not in strong neutralizing Ab response. Ross *et al.* [2001]

**No.** 987  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (SF162DeltaV2)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with protein boost  
*Strain:* B clade SF162 *HIV component:* gp140 *Adjuvant:* MF59  
**Species (Isotype)** macaque  
**References** Cherpelis *et al.* 2001a; Cherpelis *et al.* 2001b

- Two animals were immunized both intradermally and intramuscularly at weeks 0, 4, and 8 with a codon optimized DNA vector expressing the SF162V2 gp140 envelope with an intact gp120-gp41 cleavage site, and both developed lymphoproliferative responses and potent neutralizing Abs – CD8+ T lymphocytes were depleted in the animals and they were challenged with SHIV162P4 – at peak viremia, plasma viral levels in the vaccinated animals were 1 to 4 logs lower than those in the unvaccinated animals. Cherpelis *et al.* [2001b]
- HIV-1 SF162ΔV2 gp140 envelope was used in a DNA-prime plus protein-boost vaccination methodology in Rhesus macaques, the animals were depleted of their CD8+ T lymphocytes, and challenged with pathogenic SHIV(SF162P4)—the vaccinated macaques had lower peak viremia, rapidly cleared virus from the periphery, and developed delayed seroconversion to SIV core antigens relative to non-vaccinated controls. Cherpelis *et al.* [2001a]

**No.** 988  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Sarmati *et al.* 2001

- Some HIV-1 infected patients have increasing CD4 counts despite failing ARV, and CD4 levels are correlated with HIV-1 specific NABs – no correlation was found between NABs and viral load in this patients. Sarmati *et al.* [2001]

**No.** 989  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp41 (539–684 BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp41  
**Species (Isotype)** mouse (IgG)  
**References** Bai *et al.* 2000

- There is a common epitope in HIV-1 gp41, and IFNalpha and IFNbeta. Bai *et al.* [2000]

**No.** 990  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)** human (IgM)  
**References** Llorente *et al.* 1999

- Combinatorial antibody analysis by phage display and flow cytometry demonstrated that gp120 in HIV-1 negative people is recognized by IgM, but not IgG Abs – IgM Fab reactivity is observed throughout the entire sequence of HIV-1 IIIB gp120 and is characterized by low affinity binding and near germline configuration reflecting a lack of maturation of the IgM repertoire – no neutralizing activity was observed in a non-infected individual before isotope switching. Llorente *et al.* [1999]

**No.** 991  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (SF2)  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF2  
*HIV component:* gp120  
**Species (Isotype)** human (IgM)  
**References** Locher *et al.* 1999

- High risk volunteers were vaccinated with SF2 gp120 – 3 breakthrough cases were studied – SF2 neutralizing Abs were observed, but Ab titers to autologous virus were never high and took 6 months after HIV-1 infection to develop – viral loads were similar to HIV-1 infected individuals who had not been vaccinated. Locher *et al.* [1999]

**No.** 992  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (subtype A, B, C, D, CRF01)  
**Epitope**

- Subtype** A, B, C  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* formaldehyde-fixed whole-cell  
*HIV component:* gp120
- Species (Isotype)** mouse (IgG)  
**References** Nunberg 2002; LaCasse *et al.* 1999
- A retraction was printed (Science 296:1025, 2002) noting that an unknown cytotoxic effect of these complex sera accounted for a major fraction of the neutralization reported in LaCasse *et al.* [1999] Nunberg [2002]. LaCasse *et al.* [1999]; Nunberg [2002]
  - In this study, immunogens were generated that were thought to capture transient envelope-CD4-coreceptor structures that arise during HIV binding and fusion by formaldehyde-fixation of co-cultures of cells expressing HIV-1 Env and those expressing CD4 and CCR5 receptors – these cells elicited NAb in CD4- and CCR5-transgenic mice that neutralized 23/24 primary isolates from clades A-E. LaCasse *et al.* [1999]

- No.** 993  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** (B consensus)  
**Epitope**  
**Subtype** B  
**Neutralizing** P  
**Immunogen** HIV-1 infection
- Species (Isotype)** human  
**References** Morris *et al.* 2001b
- Ab responses before HAART therapy and after one year of therapy were measured in 8 individuals that were classified HAART successes, and 10 patients who were classified as HAART failures – V3 peptide antibody binding titers to the B-consensus and MN and SF2 variants, and neutralization of HIV-1 MN and four subtype B clinical isolates were tested – subjects with strong anti-V3 and NAb humoral immune responses before starting HAART were more likely to achieve sustained viral suppression to <500 copies RNA/ml on HAART – HIV-specific Ab responses declined after 1 year of successful viral suppression on HAART. Morris *et al.* [2001b]

- No.** 994  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 infection
- Species (Isotype)** human (IgG)  
**References** Pilgrim *et al.* 1997
- Sera from long-term nonprogressors(LTNP) had broader NAb against heterologous primary isolates and were more likely to neutralize the contemporaneous autologous isolate than were sera from short-term nonprogressors and normal progressors – in 4 individuals followed from acute infection, NAb were detected against the early autologous isolate by 5-40 weeks, and not detected in an additional 2 cases after 27-45 weeks. Pilgrim *et al.* [1997]

- No.** 995  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 infection
- Species (Isotype)** human  
**References** Moog *et al.* 1997
- Autologous and heterologous NAb were studied in 18 individuals who were sampled early after sero-conversion and followed longitudinally – autologous NAb were not detected in sera collected at the same time as the viruses were isolated – NAb detected against the seroconversion autologous strains were not detected one year after seroconversion, and were highly specific to the virus present at the early phase of HIV infection – heterologous neutralization of primary isolates were not detected until after 2 years. Moog *et al.* [1997]

- No.** 996  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing** yes  
**Immunogen** HIV-1 infection
- Species (Isotype)** human  
**References** Montefiori *et al.* 2001
- In 7/9 patients in whom HAART was initiated during early seroconversion, NAb to autologous strains were not found immediately following treatment interruption after 1-3 years, and Env and Gag Abs were low or undetected by ELISA indicating, that early HAART suppresses the normal antibody response to HIV-1, presumably by limiting the concentration of viral antigens needed to drive B-cell maturation – in 3 patients with a viral rebound autologous NAb rapidly appeared and correlated with spontaneous down-regulation of viremia – prolonged control of viremia after stopping treatment persisted in the absence of detectable NAb, suggesting that cellular immune responses alone can control viremia under certain circumstances – these results support the notion that virus-specific B-cell priming, combined with CD8+ CTL induction, may be beneficial for HIV-1 vaccines that aim to suppress viremia in the absence of complete protection to prevent disease and reduce the rate of virus transmission. Montefiori *et al.* [2001]

- No.** 997  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection
- Species (Isotype)** human (IgG)  
**References** Scala *et al.* 1999



- Random peptide libraries were screened using sera from HIV-infected subjects to identify mimotopes, peptides that mimic conformational or linear epitopes specifically recognized by Abs from HIV-1 infected individuals – the sera of simian SHIV-infected monkeys also recognized the specific peptides, and mice immunized with the selected peptides elicited HIV-specific Abs that neutralized HIV-1 isolates IIIB and NL4-3. Scala *et al.* [1999]

**No.** 998  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* mimotopes  
**Species (Isotype)** mouse (IgG)  
**References** Scala *et al.* 1999

- Random peptide libraries were screened using sera from HIV-infected subjects to identify mimotopes, peptides that mimic conformational or linear epitopes specifically recognized by Abs from HIV-1 infected individuals – the sera of simian SHIV-infected monkeys also recognized the specific peptides, and mice immunized with the selected peptides elicited HIV-specific Abs that neutralized HIV-1 isolates IIIB and NL4-3. Scala *et al.* [1999]

**No.** 999  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* virus-like particle (VLP) *HIV component:* Env, Gag *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (Isotype)** mouse (IgG)  
**References** Lebedev *et al.* 2000

- Virus-like particles (VLPs) in the form of spherical particles with yeast dsRNA enveloped in a polysaccharide matrix carrying the protein TBI, that contains fragments of HIV Env and Gag, were used to immunize BALB/c mice and induced specific Abs against HIV-1 as measured by ELISA with TBI. Lebedev *et al.* [2000]

**No.** 1000  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Donners *et al.* 2002

- A difference in neutralization patterns between African and European plasma is observed, especially in African women, who tended to have cross-neutralizing Abs against primary isolates. Donners *et al.* [2002]

**No.** 1001  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**References** Dianzani *et al.* 2002

- Immune complexes(ICs) in the plasma contained HIV RNA (80%-100%) in association with HIV-specific IgG NABs indicating that the HIV in the plasma of carriers is frequently composed of antibody-neutralized HIV as ICs. Dianzani *et al.* [2002]

**No.** 1002  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**References** Kimura *et al.* 2002

- Significant neutralization activity against autologous isolates was observed in 13/19 HIV+ patients at initiation of HAART therapy which persisted during therapy, increasing in one patient, and declining in one patient – 3/6 patients with no detectable NAb at the start of therapy developed NAb responses – of the four patients with increased NAb responses, three had low level viral rebounds (blips). Kimura *et al.* [2002]

**No.** 1003  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 exposed seronegative  
**Species (Isotype)** human (IgA)  
**References** Devito *et al.* 2000b

- Mucosal and plasma HIV-specific IgA that can neutralize primary isolates is present saliva (11/15 tested) and plasma (11/15) and cervicovaginal fluid (11/14) from highly exposed persistently seronegative (HEPS) individuals. Devito *et al.* [2000b]

**No.** 1004  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 exposed seronegative  
**Species (Isotype)** human (IgA)

**References** Devito *et al.* 2000a

- IgA from the genital tract, saliva and plasma from highly exposed persistently seronegative (HEPS) individuals can inhibit transcytosis of HIV-1 across a transwell system that provides a tight epithelial cell layer—50% of the IgA samples studied were able to inhibit transcytosis of at least one of two primary isolates tested, indicating this may be an important mechanism against sexual acquisition of HIV-1. Devito *et al.* [2000a]

**No.** 1005**MAb ID** polyclonal**HXB2 Location** Env**Author Location****Epitope****Subtype** A, B, D**Neutralizing** P**Immunogen** HIV-1 exposed seronegative**Species (Isotype)** human (IgA)**References** Broliden *et al.* 2001

- IgA isolated from the saliva, genital tract, and plasma of most highly exposed persistently seronegative (HEPS) sex workers in a Kenyan cohort could neutralize a B, A and D clade primary isolates and could inhibit transcytosis of HIV across a transwell model of the human mucosal epithelium. Broliden *et al.* [2001]

**No.** 1006**MAb ID** polyclonal**HXB2 Location** Env**Author Location****Epitope****Subtype** A, B, D**Neutralizing** P**Immunogen** HIV-1 exposed seronegative**Species (Isotype)** human (IgA)**References** Devito *et al.* 2002

- IgA isolated from the saliva, genital tract, and plasma of most highly exposed persistently seronegative (HEPS) Kenyan sex workers mediated broad cross-clade neutralization of primary isolates (A, B, C, D, and CRF01) – 6/10 HEPS individuals that were persistently exposed to a stable HIV+ B clade infected partner showed less breadth of neutralization, and were able to neutralize clade A and B primary isolates, but not clades C, D, or CRF01. Devito *et al.* [2002]

**No.** 1007**MAb ID** polyclonal**HXB2 Location** Env**Author Location****Epitope****Neutralizing** P**Immunogen** HIV-1 exposed seronegative**Species (Isotype)** human (IgA)**References** Mazzoli *et al.* 1999

- Serum HIV-specific IgA is present in highly exposed persistently seronegative individuals (HEPS) in the absence of serum IgG – serum IgA can be found in productively infected individuals and exposed seronegatives at similar titers – 5/15 sera from HEPS had neutralizing activity, 2 of these in purified

IgA – HIV-1 specific serum IgA concentrations declined after one year of interruption of at-risk sex. Mazzoli *et al.* [1999]

**No.** 1008**MAb ID** polyclonal**HXB2 Location** Env**Author Location****Epitope****Neutralizing** P**Immunogen** HIV-1 exposed seronegative**Species (Isotype)** human (IgA)**References** Beyrer *et al.* 1999

- HIV-specific anti-gp160 IgA is present in cervical lavage from 6/13 HIV-exposed seronegative Thai female sex workers. Beyrer *et al.* [1999]

**No.** 1009**MAb ID** polyclonal**HXB2 Location** Env**Author Location****Epitope****Subtype** B**Neutralizing****Immunogen** vaccine*Vector/Type:* DNA *Strain:* B clade HXB2/Bal**Species (Isotype)** mouse**References** Chakrabarti *et al.* 2002

- A modified gp140 (gp140ΔCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation, retained antigenic conformational determinants as defined by binding to CD4 and to MAbs 2F5, 2G12, F105, and b12, and enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002]

**No.** 1010**MAb ID** polyclonal**HXB2 Location** Env**Author Location****Epitope****Subtype** B**Neutralizing** P**Immunogen** HIV-1 infection**Species (Isotype)** human**References** Hioe *et al.* 1997a

- Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997a]

**No.** 1011  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** C  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6, B clade IIIB *HIV component:* Env  
*Adjuvant:* alpha2-macroglobin, Complete Freund's Adjuvant (CFA), GM-CSF, monophosphoryl lipid A  
**Species (Isotype)** mouse  
**References** Liao *et al.* 2002  
 • HIV-envelope peptides coupled to  $\alpha$ 2-macroglobin were much more immunogenic when formulated in monophosphoryl lipid A with GM-CSF than in complete or incomplete Freund's adjuvant or in monophosphoryl lipid A with GM-CSF alone. Liao *et al.* [2002]

**No.** 1012  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** P  
**Immunogen** vaccine  
*Vector/Type:* gp120-CD4 complex, gp140-CD4 complex *Strain:* B clade IIIB *HIV component:* gp120, gp140 *Adjuvant:* QS21  
**Species (Isotype)** macaque  
**References** Fouts *et al.* 2002  
 • gp120-CD4 and gp140-CD4 complexes were used for i.m. vaccination of rhesus macaques and neutralizing Ig was recovered using affinity chromatography using a chimeric HIV-BAL gp120 with a mimetic peptide that induces a CD4-triggered mimetic structure – the sera and affinity purified Ab were broadly neutralizing against primary X4, R5, and R5X4 isolates from multiple subtypes but did not react as well against lab-adapted isolates. Fouts *et al.* [2002]

**No.** 1013  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Pastori *et al.* 2002  
 • HAART initiated during primary infection was studied in seven patients and had different effects on NAb production—in some cases,  $\alpha$ -Env Abs were inhibited during primary infection, and in some cases strong NAbs against autologous virus were induced. Pastori *et al.* [2002]

**No.** 1014  
**MAb ID** polyclonal  
**HXB2 Location** Env

**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** chimpanzee (IgG)

**References** Moore & Burton 1999; Igarashi *et al.* 1999  
 • The rate of virus clearance in the circulation in rhesus macaques receiving a continuous infusion of cell-free viral dual-tropic virus isolate HIV-1DH12 particles in the presence and absence of virus-specific antibodies was measured – the clearance of physical and infectious viral particles is very rapid in naive animals, with half-lives ranging from 13 to 26 minutes, but clearance could be achieved with a half life of 3.9-7.2 minutes when chimpanzee neutralizing Abs were present to help to remove virions from the blood. Igarashi *et al.* [1999]  
 • polyclonal: Commentary discussing this finding noting the particularly high neutralization titer and limited breadth of the chimpanzee sera used in this study. Moore & Burton [1999]

**No.** 1015  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* gp120, gp41  
*Adjuvant:* MF59

**Species (Isotype)** human  
**References** Gupta *et al.* 2002  
 • Different HIV strains were used for different regions: gp120 MN and gp41 LAI, rgp120 SF2, protease LAI and gag LAI. Gupta *et al.* [2002]  
 • Vaccine trial protocol 022A in 150 HIV-1 uninfected adults (130 completed the study) showed high titer ALVAC vaccine in combination with gp120 was safe and immunogenic in HIV-1 negative volunteers – NAb responses were detected in 95% of vaccinees, with higher titers in recipients of sequential versus simultaneous dosing of the two vaccines and in vaccinia naive volunteers. Gupta *et al.* [2002]

**No.** 1016  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade 89.6  
*HIV component:* gp120, gp140 *Adjuvant:* Cholera toxin (CT), IL-12  
**Species (Isotype)** mouse (IgA, IgG, IgG1, IgG2a)  
**References** Albu *et al.* 2003  
**Keywords** genital and mucosal immunity, mucosal immunity, Th1, Th2

- Mice were intranasally immunized with gp120 or gp140 with IL-12 and Cholera toxin as adjuvants. Adjuvants enhanced NAb stimulation in mucosa and genital tissues and in serum. Albu *et al.* [2003] (**genital and mucosal immunity, mucosal immunity, Th1, Th2**)

No. 1017

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)**

**References** Berger 2002

**Keywords** antibody generation, immunotherapy

- This medical hypothesis proposes that HIV shares domains with human proteins, masked from the immune response as they are seen as self. They propose blocking the shared determinants on human proteins in the thymus with antibodies, to allow anti-self responses which are normally inhibited to occur in HIV+ people. Berger [2002] (**antibody generation, immunotherapy**)

No. 1018

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Subtype** A

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* virus-like particle (VLP)

*Strain:* A clade UG5.94UG018 *HIV*

*component:* Gag, gp120

**Species (Isotype)** mouse

**References** Buonaguro *et al.* 2002

**Keywords** subtype comparisons

- BALB/c mice were immunized with VLPs carrying a subtype A gp120. Humoral immune responses directed against B-clade derived Gag (p24) peptides or gp120-Env V3 loop peptide were readily induced following a multi-dose immunization with VLP particles presenting a gp120 molecule from a HIV-1 isolate of clade A. VLP-immunized mice showed autologous and heterologous (against B-clade HIV-1 IIIB strain) neutralization activity. Proliferative responses and CTL were also observed. Buonaguro *et al.* [2002] (**subtype comparisons**)

No. 1019

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Subtype** A, B, D

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* canarypox, protein *Strain:* B

clade LAI, B clade MN *HIV component:*

Env, Gag, Protease

**Species (Isotype)** human

**References** Cao *et al.* 2003

**Keywords** subtype comparisons

- 20 Ugandan seronegative individuals were intramuscularly immunized in this study with an ALVAC HIV GagPol and Env vaccine carrying B clade antigens. 3/20 of subjects produced neutralizing antibodies against the autologous HIV-1 clade B strain MN that was T-cell line adapted; 2 also had NAb reactivity against a primary B clade cell line. No NAb cross-reaction was observed with primary viral isolates UG92029 (subtype A) or UG92046 (subtype D). 4/20 had detectable CTL activity against B clade antigen, and one of these cross-reacted with A clade antigen, one with D clade. Cao *et al.* [2003] (**subtype comparisons**)

No. 1020

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp160

**Epitope**

**Neutralizing**

**Immunogen** SHIV infection

**Species (Isotype)** macaque

**References** Crawford *et al.* 1999

**Keywords** variant cross-recognition or cross-neutralization

- Neutralization assays with rsCD4, MAbs, and serum samples from SHIV-infected macaques and HIV-1 infected individuals were used to characterize the antigenic properties of the env glycoprotein of six primary isolate or TCLA SHIV variants. SHIV infected macaques could neutralize autologous virus very effectively, but serum from HXB2c or 89.6 infected animals could not neutralize heterologous SHIVs. Serum from KU infected animals could neutralize only HXB2c, and serum from 89.6PD infected animals could neutralize 89.6, 89.6P, 89.6PD and KB9 (all derived from 89.6) well. Many sera from the SHIV infected macaques could also neutralize HIV-1 strains MN and SF2. Crawford *et al.* [1999] (**variant cross-recognition or cross-neutralization**)

No. 1021

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp160

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Crawford *et al.* 1999

**Keywords** variant cross-recognition or cross-neutralization

- Neutralization assays with rsCD4, MAbs, and serum samples from SHIV-infected macaques and HIV-1 infected individuals were used to characterize the antigenic properties of the env glycoprotein of six primary isolate or TCLA SHIV variants. Serum from 9 HIV-1 infected people were tested for their ability to neutralize SHIVs. KU2 was least sensitive, 89.6, 89.6P, 89.6PD and KB9 (all derived from 89.6) were moderately susceptible, and SHIV HXB2c was less sensitive than

IIIB, the strain from which it was derived. Crawford *et al.* [1999] (**variant cross-recognition or cross-neutralization**)

- No.** 1022  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** B, C, CRF01\_AE  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* Venezuelan equine encephalitis virus (VEE) *Strain:* B clade R2 *HIV component:* gp160 $\Delta$ CT
- Species (Isotype)** rabbit, mouse (IgG)  
**References** Dong *et al.* 2003  
**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization
- Mice and rabbits were immunized with Venezuelan equine encephalitis virus (VEE) replicon system particles expressing HIV-1 Env from the clone R2 that was derived from a virus that was neutralization sensitive and isolated from an individual that made strong NAb responses. Stronger and faster NAb responses were induced with replicons expressing gp160 with the cytoplasmic tail deleted than with gp160 or gp140. NAb responses against heterologous strain SF162 were similar in BALB/c and C3H/He mice and enhanced compared to responses elicited in C57BL/6 mice. Serum from mice neutralized 5 primary clade B env proteins, a chinese clade C strain, but not a chinese clade E (CRF-1) strain. Sera from 3/3 immunized rabbits could neutralize SF162, and from 2/3 neutralized the autologous R2 strain. Dong *et al.* [2003] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - Subcutaneous or intradermal immunization with VEE replicons expressing HIV-1 R2 gp140 and with HIV-1 R2 gp160 lacking the cytoplasmic tail. Sera from 3/3 rabbits inhibited SF162 infectivity and 2/3 rabbits were able to neutralize the R2 strain. Dong *et al.* [2003]
  - C3H/He mice immunized with replicons expressing RT env protein or the VEE env vector pGP expressing either gp140 or gp160 showed cross-reactive neutralizing Ab responses to five clade B env proteins, a chinese clade C strain and weakly against a chinese clade E (CRF-1) strain. Dong *et al.* [2003]

- No.** 1023  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** multiple, M, O  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Donners *et al.* 2003  
**Keywords** assay development, assay standardization/improvement, co-receptor, kinetics, subtype comparisons

- Plasma samples from six HIV-1 + Belgians showed broad cross-neutralization ability against primary isolates from group M (subtypes A-H) and Group O. Viruses with R5, X4, and R5X4 co-receptor usage were all represented in the test panel. Kinetics of neutralization showed that NAb responses detected using a PBMC assay with a short incubation period could be lost upon extended culture. No preincubation with Ab was needed to see some inhibition of virus replication, indicating that at least partial neutralization occurs post-virus binding to target cells. Donners *et al.* [2003] (**assay development, co-receptor, kinetics, subtype comparisons, assay standardization/improvement**)

- No.** 1024  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Research Contact** Rebeca Geffin, Miami School of Medicine  
**References** Geffin *et al.* 2003  
**Keywords** autologous responses, escape, rate of progression, responses in children
- A longitudinal study of NAb responses in perinatally HIV-1 infected infants and children was undertaken, including 7 with rapid progression (RP) and 9 who did not progress rapidly (NRP). A subset of both RPs and NRPs had some plasma samples that could neutralize contemporaneous autologous viral isolates after 6 months of age, but most isolates could not be neutralized by contemporaneous plasma, only by later samples. The non-contemporaneous NABs would persist for years, had highest titers against earlier isolates, and tended to be more potent in NRP children. This study indicates that there is ongoing NAB escape in HIV-1 + children. No correlation between HIV RNA levels and Ab production was established, although this might have been complicated by treatment. Geffin *et al.* [2003] (**autologous responses, escape, responses in children, rate of progression**)

- No.** 1025  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)**  
**Research Contact** Mascola2003b  
**References** Mascola & Montefiori 2003  
**Keywords** escape, review

- This paper reviews the paper by Wei *et al.* (Nature 2003) that substantiates the notion that HIV evolves to change the number and position of glycosylation sites in Envelope and this facilitates neutralization escape *in vivo*. This NAb escape mechanism is called a glycan shield. Mascola & Montefiori [2003] (**escape, review**)

**No.** 1026

**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** macaque  
**References** Mascola 2003  
**Keywords** immunoprophylaxis, review

- This review discusses the importance and function of protective antibody responses in animal model studies in the context of effective vaccine development. SHIV models have shown protection using high levels of MAbs can prevent infection, and partial protection that can influence disease course can be obtained from modest levels of NABs. The binding properties and SHIV challenges studies conducted with infusions of combinations of MAbs b12, 2G12, and 2F5 are reviewed. Mascola [2003] (**immunoprophylaxis, review**)

**No.** 1027  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with virus-like particle (VLP) boost, fowlpoxvirus prime with virus-like particle (VLP) boost *Strain:* B clade 89.6P *HIV component:* Env

**Species (Isotype)** rabbit  
**References** Radaelli *et al.* 2003  
**Keywords** Th1, Th2

- Three different immunization protocols using two recombinant fowlpox (FP) constructs and two expression plasmids (SIV mac239 gg/pol or HIV-1 env 89.6P) for priming and VLP particles for boosting were tested for their ability to elicit neutralizing Ab and cell-mediated immune responses. NAb responses against SHIV 89.6P were elicited in all protocols tested. Plasmid DNA (pcDNA3gag/pol SIV) was more efficient than the FP vector (FPgag/polSIV) in inducing Ab responses to the gag core protein (p27). DNA plasmid followed by a VLP boost elicited a Th0 profile. Radaelli *et al.* [2003] (**Th1, Th2**)

**No.** 1028  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** B, CRF01\_AE  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Polonis *et al.* 2003  
**Keywords** co-receptor, escape, subtype comparisons

- Neutralization of 49 subtype E HIV-1 isolates from various stages of disease and 21 subtype B viruses was compared using polyclonal Ab pools and single subtype E plasmas. Non-syncytium-inducing (NSI) CRF01 (subtype E) HIV-1 isolates showed increased sensitivity to neutralization (42%) than syncytium-inducing (SI) subtype E isolates (9%). In contrast, the viral phenotype of subtype B isolates did not correlate with neutralization sensitivity. SI viruses were primarily X4 (one X4R5 was identified), NSI were R5. Low CD4+ T cell numbers in subtype E infected patients correlated with concurrent isolate resistance to neutralizing Ab responses. Polonis *et al.* [2003] (**co-receptor, escape, subtype comparisons**)

**No.** 1029  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade W61D *HIV component:* gp120, Nef, Tat  
*Adjuvant:* AS02A (oil-in-water emulsion, 3D-monophosphoryl lipid A, QS21), AS06 (CpG, aluminum hydroxide)

**Species (Isotype)** macaque (IgG)  
**References** Voss *et al.* 2003  
**Keywords** adjuvant comparison, variant cross-recognition or cross-neutralization

- Monkeys were immunized with different combinations of gp120/NefTat/SIV-Tat three times over a three-month time period and intravenously challenged with SHIV 89.6P four weeks after the last immunization. Vaccination induced anti-Tat, -Nef and -gp120 Ab responses that decreased until challenge. Neutralizing Ab responses against HIV-1 MN and HIV-1 W61D were observed. Vaccination with the combination of all three proteins reduced viral load and kept animals from a CD4+ T cell decline, preventing AIDS for more than 2.5 years. The adjuvant AS02A elicited NABs and protected from disease, while AS06 did not. gp120 alone or TatNef/SIV-Tat without gp120 could not protect from disease. Voss *et al.* [2003] (**adjuvant comparison, variant cross-recognition or cross-neutralization**)

**No.** 1030  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *Adjuvant:* QS21

**Species (Isotype)** mouse  
**References** Cunto-Amesty *et al.* 2001  
**Keywords** mimotopes, vaccine antigen design

- Concanavalin A binds to mannose/glucose, and binds to HIV-1. Con A was used to select peptide mimics of carbohydrates that bound to Con A, and the mimetic peptides were then used for BALB/c mouse immunization. Abs raised against the mimetic peptides binds to HIV+ cells, and could weakly neutralize T cell lab adapted strains. Cunto-Amesty *et al.* [2001] (**mimotopes, vaccine antigen design**)

**No.** 1031

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* E. Coli recombinant protein  
*HIV component:* gp120, gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** mouse

**References** Li *et al.* 2002

**Keywords** vaccine antigen design

- A polypeptide vaccine was designed based on a recombinant GST fusion protein containing three repeats of the 2F5 core epitope ELDKWA combined with the V3 region peptide GP-GRIFY. Abs raised in mice could recognize the peptides, sgp41, and CHO-WT cells that expressed HIV-1 Env on their surface. Li *et al.* [2002] (**vaccine antigen design**)

**No.** 1032

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Montefiori *et al.* 2003

**Keywords** acute/early infection, autologous responses, escape

- AC10 is a subject who was given treatment early after infection, and had a viral rebound after cessation of therapy, which then declined to a low level. The polyclonal sera from AC10 could potentially neutralize the rebound virus, and NAb escape followed with a neutralizing response against the escape variant and subsequent escape from that response. Viral loads remained low in this subject despite escape. The rebound isolate that was potentially neutralized by autologous sera was not particularly neutralization sensitive, as it resisted neutralization by sCD4 and MAbs IgG1b12, 2G12 and 2F5, and was only moderately sensitive to sera from other HIV+ individuals that had high titers of NAb to TCLA strains. Montefiori *et al.* [2003] (**autologous responses, acute/early infection, escape**)

**No.** 1033

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (DH012)

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein

**Species (Isotype)** chimpanzee

**References** Zhu *et al.* 2003

**Keywords** vaccine-specific epitope characteristics

- This study compares the immunogenicity of the HIV DH012 strain in chimpanzees during a natural infection with DH012 vaccinations. Naturally infected chimpanzees have sera containing potent anti-DH012 neutralization Abs, but the primary epitope is a discontinuous conformational epitope called CEV that involves the V1/V2 region, the bridging sheet, and the V3 loop. Abs that are raised upon gp120 vaccination, in contrast, are primarily against V3. DH012 has preserved the epitopes for the MAbs IgG1b12, 2G12, 17b, however natural DH012 infection in chimpanzees and DH012 gp120 vaccination in guinea pigs does not give rise to Abs against these epitopes. Zhu *et al.* [2003] (**vaccine-specific epitope characteristics**)

**No.** 1034

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing** yes

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Aasa-Chapman *et al.* 2004

**Keywords** acute/early infection, autologous responses

- Neutralizing Ab responses to autologous virus envelopes were studied in four acutely HIV-1 infected, treatment-naive, homosexual men (MM1, MM2, MM4 and MM8). Detection of gp120 antibodies was rapid using ELISPOT, within a few weeks, but detection of neutralizing antibodies took between 3 and 16 months, precluding involvement of detectable NAb with resolution of viremia. Heterologous NAb responses arose even later, by 3 months or more, suggesting gradual broadening of the immune response. Aasa-Chapman *et al.* [2004] (**autologous responses, acute/early infection**)

**No.** 1035

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (V3) (IIIB)

**Epitope**

**Subtype** B

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB, B clade MN *HIV component:* gp120 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** rabbit, guinea pig

**References** Berman *et al.* 1992

**Keywords** vaccine-specific epitope characteristics

- Abs derived from immunizations of rabbits and guinea pigs with either IIIB- or MN-gp120 were compared. Both could block gp120 binding to CD4, and this activity was strain-specific. Antisera from IIIB-rgp120 immunizations could only

neutralize displayed homologous virus, while sera from MN-rgp120 rabbit vaccinations could neutralize MN 3/8 additional tested viruses. Berman *et al.* [1992] (**vaccine-specific epitope characteristics**)

**No.** 1036  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env (YU-2)  
**Epitope**  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* DNA with CMV promotor, DNA prime with protein boost *Strain:* B clade YU2 *HIV component:* gp140 *Adjuvant:* monophosphoryl lipid A, trehalose dicorynomycolate  
**Species (Isotype)** mouse (IgG)  
**References** Bower *et al.* 2004  
**Keywords** adjuvant comparison, vaccine antigen design

- DNA vaccines encoding an uncleaved form of YU-2 gp140 stabilized with a synthetic trimerization domain isolated from the fibritin (FT) protein of the T4 bacteriophage and fused to murine C3d as a molecular adjuvant, could induce low titers of neutralizing antibodies against primary isolates HIV-1 YU-2 and HIV-1 ADA. DNA was administered by gene gun immunization to BALB/c mice, protein boost was performed by intraperitoneal injection. C3d is a component of the innate immune system that can serve as a molecular adjuvant and had been previously shown to enhance immunogenicity. Bower *et al.* [2004] (**adjuvant comparison, vaccine antigen design**)

**No.** 1037  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** multiple  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade IIIB, A clade UG37, B clade HAN2, D clade UG21, F clade BR29 *HIV component:* gp140, gp120ΔV1, V2, and V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)  
**Species (Isotype)** rabbit  
**References** Jeffs *et al.* 2004  
**Keywords** subtype comparisons, vaccine antigen design

- A set of oligomeric envelope proteins were made from six primary isolates for potential use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. Polyclonal sera raised in rabbits against the A, B, D and F antigens, which were deemed pure enough for immunization, as well as IIIB and

IIIB with the V1, V2 and V3 loops deleted, cross-bound the other antigens, so shared epitopes across clades, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design, subtype comparisons**)

**No.** 1038  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** B, CRF01\_AE  
**Neutralizing**  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* protein *Strain:* B clade MN, B clade GNE8, E clade CM244 *HIV component:* gp120 *Adjuvant:* aluminum hydroxide  
**Species (Isotype)** human  
**References** Lee *et al.* 2001  
**Keywords** assay development, subtype comparisons, vaccine antigen design, vaccine-induced epitopes

- An assay was developed that characterizes antibody binding to primary isolates, and using this system there was a correlation between binding activity and neutralization by sera from HIV-infected people and gp120 vaccinated individuals. The magnitude and breadth of oligomeric, cell surface gp120 binding Abs induced by HIV-1 subtype B vaccines was characterized. The responses in people vaccinated with mono- and bivalent rgp120 vaccines (AIDSVAX B and AIDSVAX B/B AIDSVAX B/E) indicated that increasing the number of antigens increased the cross-binding activities, in support of polyvalent vaccines. Lee *et al.* [2001] (**assay development, vaccine antigen design, vaccine-induced epitopes, subtype comparisons**)

**No.** 1039  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* gp120-MAb A32 complex *Strain:* B clade 89.6, B clade BaL *HIV component:* gp120-Mab complex *Adjuvant:* Cholera toxin (CT), Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA), Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** guinea pig  
**References** Liao *et al.* 2004  
**Keywords** vaccine antigen design

- A32-rgp120 complexes opened up the CCR5 co-receptor binding site, but did not induce neutralizing antibodies with greater breadth among B subtype isolates than did uncomplexed rgp120 in vaccinated guinea pigs. The vaccine that



gave the greatest breadth comparing A32-rgp120 BaL, A32-rgp120 89.6, rgp120 BaL, and rgp120 89.6, was the uncomplexed rgp120 BaL, as it neutralized 9/14 B clade isolates tested (60%). Liao *et al.* [2004] (**vaccine antigen design**)

**No.** 1040  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (JRFL)  
**Epitope**  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade JRFL  
*HIV component:* gp120 *Adjuvant:* C3d fusion  
**Species (Isotype)** humanized mouse (IgG)  
**References** Liu *et al.* 2004  
**Keywords** adjuvant comparison

- BALB/c mice were immunized with codon-optimized or C3d-fused DNA vaccine constructs and analyzed for their ability to elicit humoral and cell-mediated immune responses. Each strategy increased binding and gave rise to earlier appearance of neutralizing antibody responses against IIIB and MN viruses, but the combination did not act synergistically. C3d and codon optimization also gave enhanced CD8+ T cell responses to the epitope SIHIGPGRAFYTTGE. Liu *et al.* [2004] (**adjuvant comparison**)

**No.** 1041  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env (SF2)  
**Epitope**  
**Subtype** multiple  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF2  
*HIV component:* gp120 *Adjuvant:* aluminum hydroxide, Incomplete Freund's Adjuvant (IFA), MF59, Other  
**Species (Isotype)** baboon  
**References** Haigwood *et al.* 1992  
**Keywords** adjuvant comparison, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- Baboons were given intramuscular immunization with env 2-3 SF2 (aa Ile-26 to Ala-510) or rgp120SF2. Native, glycosylated rgp120 SF2, gave a broader range of heterologous neutralizing Ab responses than denatured, non-glycosylated env 2-3 SF2. Repeated immunizations with the native rgp120 gave rise to weak but detectable NAb against two African strains, NDK and ZR6. IFA/MTP-PE gave the highest titer antibodies of many adjuvant combinations tested. Haigwood *et al.* [1992] (**adjuvant comparison, vaccine antigen design, variant cross-recognition or cross-neutralization, vaccine-specific epitope characteristics**)

**No.** 1042  
**MAb ID** polyclonal

**HXB2 Location** Env  
**Author Location** Env (89.6)  
**Epitope**  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** vaccine  
*Strain:* B clade 89.6 *HIV component:* gp140, gp160, gp160ΔV3, gp140ΔV3  
**Species (Isotype)** macaque, mouse  
**References** Lorin *et al.* 2004  
**Keywords** vaccine antigen design, variant cross-recognition or cross-neutralization

- Mice susceptible to MV infection were intraperitoneally immunized with native HIV-1 89.6 env gp160 and gp140 and ΔV3 HIV-1 89.6 mutants expressed in live attenuated Schwarz measles vector (MV). The gp160ΔV3 construct raised more cross-reactive NAb to primary isolates than did native gp160, and sera from the gp160ΔV3 animals neutralized SHIV 89.6, clade B strains Bx09, 92US660 and 92US714, and clade A virus 3253 but not to clade B 92HT593, at a 1:30 dilution. A HIVIG/2F5/2G12 combination was used as a positive control and could neutralize all isolates. The vaccine constructs had an additional 2F5 MAb epitope, ELDKWAS, but responses were not directed towards this epitope. Mice and macaques could raise anti-HIV responses in mice and macaques with pre-existing MV immunity. Lorin *et al.* [2004] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)

**No.** 1043  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** McCaffrey *et al.* 2004  
**Keywords** antibody binding site definition and exposure, vaccine antigen design

- Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) and adjacent to the C-terminal end of the V3 loop (GM329 C3) increased neutralization susceptibility to both sera, but the loss of sites in C2, C4, and V5 did not alter neutralization susceptibility. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure, vaccine antigen design**)

**No.** 1044  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (HXBc2)  
**Epitope**  
**Subtype** B  
**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* Con A-NS *Strain:* B clade HXBc2 *HIV component:* Env

**Species (Isotype)** macaque (IgA, IgG)

**References** Miyake *et al.* 2004

**Keywords** genital and mucosal immunity

- Intranasal immunizations of three macaques with SHIV-nanospheres (SHIV-NS) induced vaginal anti-HIV-1 gp120 IgA and IgG antibodies. After intra-vaginal challenge with SHIV KU-2, 1/3 control animals and 1/3 SHIV vaccinated animals were infected, but the SHIV vaccinated animals had low viral loads that fell to undetectable levels. After intravenous re-challenge, all animals were infected, but SHIV immunized animals had lower viral loads. Miyake *et al.* [2004] (**genital and mucosal immunity**)

**No.** 1045

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp41 (HXB2)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**References** Opalka *et al.* 2004

**Keywords** assay development, assay standardization/improvement

- An antigen panel representing different regions of gp41 was generated, and sera from 23 individuals were screened. Anti-gp41 titers were very high, and sera bound to many regions of gp41, there were no immunologically silent regions. Many individuals had broad responses to diverse regions. High titer responses tended to focus on the N-heptad, C-heptad and 2F5-4E10 regions, but there was no correlation between neutralization capacity of sera and the particular peptides recognized. Opalka *et al.* [2004] (**assay development, assay standardization/improvement**)

**No.** 1046

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Research Contact** Abraham Pinter, Public Health Research Institute, Newark, NJ, 07103. pinter@phri.o

**References** Pinter *et al.* 2004

**Keywords** variant cross-recognition or cross-neutralization

- V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162

pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 28 sera were tested – 24/28 sera gave greater than 90% neutralization of SF162 at dilutions of 1:180, while only 2/28 could give 90% neutralization of JRFL, and only 9/28 gave 50% neutralization at dilutions of 1:180. A chimera with SF162 V1V2 in a JRFL Env backbone was neutralization sensitive to most sera at a comparable level to SF162 Env, and in some cases the JRFL-SF162 V1V2 chimera was even more sensitive than JRFL. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)

**No.** 1047

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env (gp160)

**Epitope**

**Subtype** multiple

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* DNA, DNA prime with protein boost *Strain:* B clade LAI, A clade 92UG031, C clade 92BR025 *HIV component:* gp160 *Adjuvant:* GM-CSF

**Species (Isotype)** mouse (IgG)

**References** Rollman *et al.* 2004

**Keywords** adjuvant comparison, enhancing activity, Th1, Th2, vaccine antigen design, variant cross-recognition or cross-neutralization

- Vaccination of mice with subtype B Env raised antibodies primarily against subtype B alone, while A+B+C clade Envs raised antibodies that could neutralize the autologous B, C strains, and weakly neutralize the A strain. Serum IgG responses to gp120s including all gp120 variable regions were induced in animals vaccinated with subtypes A, B and C of HIV-1 gp160 with rGM-CSF as adjuvant. Boosting with rgp160 with CpG-ODN enhanced IgG responses, shifted the Th1/Th2 to be more balanced, and these animals made both IgG and Ig2a responses and had expanded recognition of constant regions. The B clade vaccine was LAI, and the A and C clade vaccines were actually V1-V5 of the A and C strains cloned into a LAI backbone. gp41 peptides were also recognized by sera. T cell responses to the multi-clade vaccine had enhanced cross-reactive CD4 T-cell proliferative responses, but diminished gamma IFN CD8 T-cell responses. Rollman *et al.* [2004] (**adjuvant comparison, enhancing activity, vaccine antigen design, variant cross-recognition or cross-neutralization, Th1, Th2**)

**No.** 1048

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade IIB *HIV component:* gp120 *Adjuvant:* C3d fusion

**Species (Isotype)** mouse (IgG, IgG2a)

**References** Toapanta & Ross 2004

**Keywords** adjuvant comparison, Th1, Th2

- Mice [C57BL/6 (H-2b), BALB/c (H-2d), C3H/H3 (H-2k) and CD-1 Swiss] were vaccinated DNA carrying with 2 or 3 complement C3d genes fused to secreted sgp120. Responses were enhanced with C3d, particularly in outbred mice. sgp120-C3d-DNA vaccination induced a primarily IgG1 anti-Env Ab response in inbred mouse strains, while outbred mice had mixed IgG1/IgG2a responses; similarly IL4 (Th2) T-cell responses were observed in inbred mice, and mixed IL4 and IFN gamma (Th1/Th2) responses were observed in outbred mice. An increased avidity maturation of anti-Env Abs in outbred mice was also observed. Toapanta & Ross [2004] (**adjuvant comparison, Th1, Th2**)

**No.** 1049

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* canarypox prime with gp120 boost *Strain:* B clade LAI, B clade MN  
*HIV component:* Gag, gp120, Protease

**Species (Isotype)** human (IgA, IgG)

**References** Wright *et al.* 2004

**Keywords** genital and mucosal immunity, vaccine antigen design

- HIV-1 specific responses were seldom detected after systemic or mucosal vaccination with HIV gp120 in a canarypox vector with a rgp120 boost. A limited IgA and CTL response was observed after rectal vaccination, but overall, canary pox virus was not an effective mucosal immunogen. Wright *et al.* [2004] (**genital and mucosal immunity, vaccine antigen design**)

**No.** 1050

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env (735–752)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** human, rabbit

**References** Kennedy *et al.* 1986

**Keywords** assay standardization/improvement

- Rabbits intramuscularly immunized with peptide KLH ("HTLV-III aa 735-752") produced peptide-specific, serum Ab responses. In an ELISA, AIDS patient derived antisera tested positive for gp41-specific Ab. Kennedy *et al.* [1986] (**assay standardization/improvement**)

**No.** 1051

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection, vaccine

**Species (Isotype)** human

**References** Zolla-Pazner 2004

**Keywords** review, vaccine antigen design

- This review summarizes neutralizing epitopes on Env and their use as vaccine antigens. Most antibodies are not neutralizing, and while some antibodies directed to conserved domains can neutralize the virus, these are generally poorly immunogenic. Variable loops do not elicit much cross-reactive neutralization, although the stem regions of these loops are more conserved so may have some promise. Polyclonal pooled sera from infected people can generally neutralize heterologous virus, suggesting that neutralizing epitopes are yet to be discovered. Polyvalent vaccine design is considered key. Zolla-Pazner [2004] (**vaccine antigen design, review**)

**No.** 1052

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** yes

**Immunogen** vaccine

*Strain:* B clade IIIB *HIV component:* gp120, gp160 *Adjuvant:* aluminum hydroxide

**Species (Isotype)** human, chimpanzee

**References** Berman *et al.* 1994

**Keywords** variant cross-recognition or cross-neutralization

- Antisera derived from human or chimpanzee immunized with IIIB-rgp120 showed broad cross-reactivity to HIV-1 isolates MN, IIIB, JRcsf and NY-5 (subtype B), Z6 (subtype D), A244 (subtype E) and Z321 (subtype A). Sera of IIIB-rgp120 chimpanzees cross-reacted with 6/8 V3 peptides derived from HIV-1 isolates (MN, NY5, SF2, RF, CDC4 and IIIB). Human sera only recognized 1/8 V3 peptides, HIV-1 MN. The magnitude, duration, avidity and half-life of IIIB-rgp120-specific Ab-responses were species specific. Sera derived from IIIB-rgp120-immunized humans and chimpanzees inhibited binding of both IIIB- and MN-derived rgp120 to cell-surface CD4. Berman *et al.* [1994] (**variant cross-recognition or cross-neutralization**)

**No.** 1053

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (V3)

**Epitope**

**Subtype** A

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* hepatitis B surface antigen lipoprotein particles (HsBAg) *Strain:* A clade *HIV component:* CD4BS, V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** mouse

**References** Cruz *et al.* 2004

**Keywords** variant cross-recognition or cross-neutralization

- Vaccinations with either the subtype A V3 consensus in a Hepatitis B carrier protein, or a multiple antigen peptide (MAP) construct (mixotope) carrying some 5000 V3s representing the diversity of subtype A V3 loops, were compared. Each was combined with a C4 peptide spanning a region involved in CD4 binding. BALB/c mice were used for immunization. The consensus V3 gave higher and more cross-reactive responses than the mixotope. The mixotope response was restricted to the most conserved region of V3, while the consensus antibodies tended to recognize heptamers representing both sides and the tip of the loop. Antibodies against the C4 region were also raised. Cruz *et al.* [2004] (**variant cross-recognition or cross-neutralization**)

**No.** 1054

**Mab ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* DNA with CMV promotor, modified vaccinia Ankara (MVA) *Strain:* B clade IIIB *HIV component:* gp120 *Adjuvant:* Cholera toxin (CT)

**Species (Isotype)** mouse (IgA, IgG, IgG1)

**References** Gherardi *et al.* 2004

**Keywords** adjuvant comparison, genital and mucosal immunity

- Env-specific IgG and IgA Abs were detected in vaginal washings of BALB/c mice (H-2Dd) following intranasal immunization of rMVA + CT in both MVA/MVA and DNA/MVA schemes. Coadministration of CT as adjuvant resulted in an increased responses. Gherardi *et al.* [2004] (**adjuvant comparison, genital and mucosal immunity**)

**No.** 1055

**Mab ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** B

**Neutralizing** yes

**Immunogen** SHIV infection

**Species (Isotype)** macaque

**References** Montefiori *et al.* 1998

**Keywords** variant cross-recognition or cross-neutralization

- Neutralizing antibody responses in rhesus macaques infected with SHIV variants HXB2, 89.6, and 89.6PD were studied. The SHIV infections resulted in induction of high-titer neutralizing Abs to homologous SHIV and HIV-1 strains; heterologous NAb responses were infrequent and only detected after 40 weeks of infection. Montefiori *et al.* [1998] (**variant cross-recognition or cross-neutralization**)

**No.** 1056

**Mab ID** polyclonal

**HXB2 Location** Env

**Author Location** gp160 (IIIB)

**Epitope**

**Subtype** B

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* DNA prime with gp160 boost

*Strain:* B clade IIIB *HIV component:*

gp160 *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-12

**Species (Isotype)** macaque

**References** Rasmussen *et al.* 2002

**Keywords** adjuvant comparison, vaccine-induced epitopes

- DNA prime vaccinations by intradermal or gene-gun delivery were given to neonatal macaques, with or without IL-12, followed by boosting with gp160, or else gp160 was given without the DNA prime. Many of the animals had neutralizing antibodies against autologous Env, and no CTL was detected prior to challenge after DNA inoculation. Autologous SHIV-vpu+ challenge was contained in 4/15 DNA prime-gp160 boost-vaccinated macaques and in 3/4 animals only receiving gp160. Six animals that contained virus were rechallenged with autologous virus, and the virus was rapidly cleared. After an additional challenge with heterologous pathogenic SHIV 89.6P, 4/6 maintained low or limited viral infection and normal CD4 counts. Two animals gave evidence of Gag specific CTL and proliferative responses after pathogenic SHIV challenge with 89.6P, with no other evidence of infection. Rasmussen *et al.* [2002] (**adjuvant comparison, vaccine-induced epitopes**)

**No.** 1057

**Mab ID** polyclonal

**HXB2 Location** Env

**Author Location** gp140 (SF162)

**Epitope**

**Subtype** B

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* DNA prime with protein boost

*Strain:* B clade SF162 *HIV component:* gp140, gp140ΔV2

**Species (Isotype)** macaque

**Ab Type** gp120 C5, gp120 C1-C2, gp120 CD4BS, gp120 V3, gp120 V1-V2

**References** Srivastava *et al.* 2003

**Keywords** vaccine antigen design, vaccine-induced epitopes

- Vaccination of macaques with SF162gp140 was compared with vaccination with SF162 deltaV2gp140. V1, V2, V3, CD4BS, C1 and C2 antibodies were elicited by the intact SF162, and the antibodies were able to neutralize some heterologous strains. Deletion of the V2 loop altered the response so that there was a higher ratio of CD4BS antibody made relative to V3 antibody, but did not increase overall amount of CD4BS antibodies. Antibodies against C5 were also elicited by the deltaV2 construct. Overall, the deltaV2 construct was

better able to raise antibodies that could cross-neutralize heterologous strains. Using a cleaved versus fused form of gp120 altered the ratio of C1 to C5 antibodies raised, with more C5 response to the fused form. Srivastava *et al.* [2003] (**vaccine antigen design, vaccine-induced epitopes**)

**No.** 1058  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (SF2)  
**Epitope**  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* protein *Strain:* B clade SF2  
*HIV component:* gp120 *Adjuvant:* aluminum hydroxide, Incomplete Freund's Adjuvant (IFA), muramyl-dipeptide base adjuvant (Syntex)  
**Species (Isotype)** human, baboon  
**References** Steimer & Haigwood 1991  
**Keywords** adjuvant comparison, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- Immunization with native glycosylated rgp120SF2 produced Abs directed against linear and conformational epitopes. Denatured, deglycosylated env2-3 (SF2) produced Abs against only linear determinants. Sera from 8/8 rgp120SF2 vs 3/8 env2-3SF2 immunized baboons cross-neutralized HIV-MN. Only 5/8 rgp120SF2 vaccinated animals had neutralizing activity against HIV-HTLV-IIIB and HIV-BRU. Abs from infected people who reacted with rgp120SF2 showed broad cross-neutralization of HIV-1MN, HIV-BRU, HIV-Zr6 and HIV-SF2 isolates, in comparison to env2-3(SF2)immunization, which only neutralized HIV-1 MN. Stronger neutralization potency of Ab responses was observed in baboons using Alum and MF101 as adjuvants. Steimer & Haigwood [1991] (**adjuvant comparison, vaccine antigen design, variant cross-recognition or cross-neutralization, vaccine-specific epitope characteristics**)

**No.** 1059  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)**

**References** Balzarini 2005  
**Keywords** antibody binding site definition and exposure

- Author hypothesizes that resistance to drugs that target glycosylation sites of gp120 might stimulate deletions within the glycan shield, thus exposing novel epitopes that enhance neutralization susceptibility. Balzarini [2005] (**antibody binding site definition and exposure**)

**No.** 1060  
**MAb ID** polyclonal  
**HXB2 Location** Env

**Author Location** gp120 (V3)  
**Epitope**  
**Subtype** multiple  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 V3  
**References** Barin *et al.* 2005  
**Keywords** acute/early infection, assay development

- A combination of 4 antigenic regions was used to differentiate between early (<180 days) and chronic infection. These regions were: p24; the gp41 peptide spanning the immunodominant epitope (IDE) of gp41, RVAVERYLKDQQLLGIWGCSGKICTTAV, and a subtype D version of this peptide; 5 V3 consensus peptides including A, B, C, D, and CRF01-AE; and Integrase. V3 and the IDE provide the best discrimination, with >20 fold higher levels in chronic infection when assayed by EIA using dried serum spots. Antibodies to Integrase and p24 were not as distinctive, and people tend to lose, not increase, responses to p24 over time. This assay can be used to identify samples from early infection with high sensitivity and specificity. Barin *et al.* [2005] (**assay development, acute/early infection**)

**No.** 1061  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Subtype** A  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* virus-like particle (VLP)  
*Strain:* A clade 94UG018 *HIV component:* anchored gp120  
**Species (Isotype)** mouse (IgA, IgG)  
**References** Buonaguro *et al.* 2005  
**Keywords** vaccine antigen design, variant cross-recognition or cross-neutralization

- The impact of vaccination routes was studied in BALB/c mice for clade A gp120 in VLPs. I.n. and i.p. vaccination gave a systemic and mucosal IgG and IgA response, and a CTL response. Higher specific IgA titers were detected in i.n. vaccinated mice, and CTL responses were stronger in the i.p. group. The oral route did not induce NAb responses. gp120-Env (V3 loop, TRPYNNTRQSTHIGPGQALYTTNIIGDIRQAHC) specific IgG and IgA Ab were detected at 1-2-dilution lower dilutions than p24 Abs. Neutralizing activity (>50%) against the autologous clade A Ugandan and a heterologous clade B Italian field isolate was observed. No adjuvants were used. Buonaguro *et al.* [2005] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)

**No.** 1062  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** multiple  
**Neutralizing**

**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* natural variants *HIV component:* gp140

**Species (Isotype)** rabbit

**Ab Type** RT thumb domain

**References** Dong *et al.* 2005

**Keywords** vaccine antigen design, variant cross-recognition or cross-neutralization

- 2F5 recognizes the epitope ELDKWA, but does not neutralize viruses carrying the commonly found mutated epitope variants: ELDeWA, ELDSWA, ELDNWA, ELdqWA, ELdtWA, or ELnKWA. Peptide cocktails containing ELDKWA, ELnKWA, ELDeWA, and ELkWA elicit polyclonal antibodies in rabbits that can bind to all of the natural variants that are escape variants for 2F5 expressed in gp41 via WB, as well as ELDrWA. Dong *et al.* [2005] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)

**No.** 1063

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** multiple

**Neutralizing**

**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* gp41 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** rabbit

**References** Dong *et al.* 2005

**Keywords** escape, vaccine antigen design, variant cross-recognition or cross-neutralization

- 2F5 recognizes the epitope ELDKWA, but does not neutralize viruses carrying the commonly found mutated epitope, ELDeWA, ELDSWA, ELDNWA, ELdqWA, ELdtWA, or ELnKWA. Peptide cocktails containing ELDKWA, ELnKWA, ELDeWA, and ELkWA, elicit polyclonal antibodies in rabbits that can bind to all of the natural variants that are escape variants for 2F5 expressed in gp41 via WB, as well as ELDrWA. Dong *et al.* [2005] (**vaccine antigen design, variant cross-recognition or cross-neutralization, escape**)

**No.** 1064

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Subtype** CRF02\_AG

**Neutralizing** no

**Immunogen** vaccine  
*Vector/Type:* virus-like particle (VLP), DNA prime with modified vaccinia Ankara (MVA) boost *Strain:* CRF02 IC0928 *HIV component:* Env, Gag, Pol

**Species (Isotype)** macaque (IgG)

**References** Ellenberger *et al.* 2005

**Keywords** vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- Macaques were given a Gag-Pol-Env DNA prime followed by a MVA boost, comparing two DNA constructs, one that resulted mature VLPs with processed Gag (IC48) and one that had a point mutation in Gag that resulted in immature VLPs (IC1-90). Both vaccines gave antibody and T-cell responses to Env and Gag, although negligible neutralizing antibody responses were found. Autologous virus is difficult to neutralize, but the antibodies in the vaccinated macaques also did not neutralize the laboratory adapted B clade MN strain. Ellenberger *et al.* [2005] (**vaccine antigen design, variant cross-recognition or cross-neutralization, vaccine-specific epitope characteristics**)

**No.** 1065

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** A, B, C

**Neutralizing** P

**Immunogen** vaccine  
*Vector/Type:* DNA, adenovirus *Strain:* B clade HXB2, A clade 92RW020, C clade 97ZA012 *HIV component:* gp140ΔCFI

**Species (Isotype)** guinea pig

**Ab Type** gp120 V3

**References** Chakrabarti *et al.* 2005

**Keywords** vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- Guinea pigs were immunized with a hybrid HXB2/BaL Env (HIV HXB/BaL gp140δCFI, clade B) in which the tip of the V3 loop (GPGR) was replaced with the 2F5 epitope LELDKWAS. 2F5 bound to the Env that carried the V3-replacement 2F5 epitope, but antibodies against this construct only neutralized the X4-tropic lab adapted HIV strain IIIB, and not CCR5-HIV BaL or SF162 isolates. This immunogen, a single B clade immunogen, and a mixture of A + B + C clade envelopes, were compared. The single B clade immunogen had neutralizing activity against some B clade viruses. The A+B+C mixture was found to maintain the B clade responses, while eliciting NABs with greater breadth when tested against a panel 19 A, B and C clade primary isolates. Chakrabarti *et al.* [2005] (**vaccine antigen design, variant cross-recognition or cross-neutralization, vaccine-specific epitope characteristics**)

**No.** 1066

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** vaccine  
*Vector/Type:* virus-like particle (VLP) *Strain:* B clade BaL *HIV component:* Env, Gag *Adjuvant:* block copolymer CRL8623

**Species (Isotype)** guinea pig

**References** Hammonds *et al.* 2005

**Keywords** adjuvant comparison, vaccine antigen design

- Adjuvanted (either with a block copolymer or with a CpG aluminum hydroxide adjuvant) pseudovirions and with a recombinant gp120 boost gave significant gp120-specific NAb responses to autologous virus relative to pseudoviruses alone and to 2/5 additional primary isolates (SS1196 and Pvo) tested. Hammonds *et al.* [2005] (**adjuvant comparison, vaccine antigen design**)

**No.** 1067

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* gp120 *Adjuvant:* C3d fusion, Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** mouse (IgG)

**References** Koch *et al.* 2005

**Keywords** adjuvant comparison

- Fusion of C3d repeats and the addition of Ribi adjuvant to gp120 variant glycoprotein (gp120 $\delta$ C1/C5(C3d)<sub>2</sub>) enhanced gp120-specific Ab responses, but Ribi alone gave almost comparable enhancement. Thus C3d as an adjuvant may be of particular value when used alone in conditions where avoiding denaturation and preservation of the native structure is important. Koch *et al.* [2005] (**adjuvant comparison**)

**No.** 1068

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env (JRFT)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* adenovirus *Strain:* B clade JRFL *HIV component:* Gag, gp140

**Species (Isotype)** macaque

**References** Liang *et al.* 2005

**Keywords** vaccine antigen design, vaccine-induced epitopes

- 4/4 Mamu-A\*01-negative rhesus monkeys that were vaccinated with gp140 and challenged intravenously with SHIV-89.6P produced significant neutralizing Ab titers by day 28 relative to other challenge groups, even though no pre-challenge NAb was detected, suggesting the existence of prechallenge memory neutralizing Ab responses. The viral set point was associated with the strength of the cellular immune response to Gag and Env, but not to Tat. Liang *et al.* [2005] (**vaccine antigen design, vaccine-induced epitopes**)

**No.** 1069

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env (MN)

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Raviv *et al.* 2005

**Keywords** vaccine antigen design

- Retrovirus inactivation for vaccine antigen delivery was explored through lipid modification by hydrophobic photoinduced alkylating probe 1.5 iodonaphthylazide (INA). The viral proteins were shown to be structurally intact in the treated non-infectious virus, through the preservation of antibody binding sites for polyclonal anti-gp120 serum, and for broadly neutralizing MAbs 2G12, b12 and 4E10, although the modifications of the lipid disabled viral infection. Raviv *et al.* [2005] (**vaccine antigen design**)

**No.** 1070

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env (gp160)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**References** Bettaieb *et al.* 1992

**Keywords** mimics

- gp160-specific Abs were detected in platelet eluates from HIV-1 infected patients with immunologic thrombocytopenia purpura (ITP). One patient with high titer anti-gp160/120 Abs had IgG that bound specifically to both gp160/120 and to platelet GPIIb/IIIa, apparent molecular mimicry. The cross-reactive epitope on gp120 has not been defined, however a conformational aspect and/or glycosylation is likely to be involved. Bettaieb *et al.* [1992] (**mimics**)

**No.** 1071

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)**

**References** Rossi *et al.* 1989

**Keywords** mother-to-infant transmission

- Abs that bound to gp120 peptides were found to correlate with lack of transmission in infants less than 6 months old and born to HIV+ mothers. Maternal Abs to these same peptides were also enriched in mothers that did not transmit. Rossi *et al.* [1989] (**mother-to-infant transmission**)

**No.** 1072

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env (Consensus B)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade consensus, B clade CAAN5342, B clade WITO4160  
*HIV component:* Env

**Species (Isotype)** guinea pig

**Research Contact** Beatrice Hahn, University of Alabama, Birmingham, bhahn@uab.edu

**References** Kothe *et al.* 2007

**Keywords** antibody binding site definition and exposure, co-receptor, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Four consensus B Env constructs: full length gp160, un-cleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective un-cleaved version mediated infection using the CCR5 co-receptor. DNA vaccinations of the four constructs were compared to two wildtype B clade isolates, CAAN5342 and WITO4160. The binding antibody titers elicited by the consensus proteins were 20 to 40 fold higher than to the two wildtype strains. ConB gp145 emerged as the immunogen with the greatest breadth and magnitude of responses, WITO4160 the worst. Con B gp145 and gp160 elicited significantly more potent antibodies than the wild type vaccines against a panel of easier to neutralize tier 1 viruses, but limited neutralization of tier 2 viruses was observed with any of the immunogens. Kothe *et al.* [2007] (**antibody binding site definition and exposure, co-receptor, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization**)

No. 1073

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** A

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Blish *et al.* 2007

**Keywords** acute/early infection, neutralization, subtype comparisons

- 15 Pseudovirus from Envs taken from subtype A infected individuals early in infection had highly variable sensitivity to autologous and heterologous plasma and to sCD4. No patterns of subtype specificity were observed in plasma pools obtained from individuals infected with subtypes A, B, C or D. The Envelopes were generally sensitive to the CCR5 inhibitors PSC-RANTES and TAK-779. Blish *et al.* [2007] (**neutralization, acute/early infection, subtype comparisons**)

No. 1074

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Subtype** A, B

**Neutralizing** P

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**References** Dhillon *et al.* 2007

**Keywords** neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- Neutralizing Ab specificities in broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals were characterized. Broadly neutralizing activity could exclusively be assigned to the IgG fraction. Abs directed against V1, V2 and V3 and gp41 MPER epitopes were shown not to account for the neutralizing activity, and neutralization was found to result from more than one specificity. These polyspecific cross-neutralizing sera could neutralize clade A, B, C, D and CRF01 AE viruses. Dhillon *et al.* [2007] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1075

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** C

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4i, gp41 MPER (membrane proximal external region)

**References** Gray *et al.* 2007

**Keywords** acute/early infection, antibody interactions, autologous responses, neutralization, variant cross-recognition or cross-neutralization

- This study of 14 individuals infected with subtype C HIV-1 showed that they developed a potent autologous NAb response between 3 and 12 months of infection. The magnitude of this response was associated with shorter V1-V5 envelope lengths and fewer glycosylation sites. Very limited heterologous viral neutralization was observed during the first year of infection. Abs to CD4i epitopes were found in most patients, while MPER antibodies developed later and in fewer individuals. Abs to CD4i or MPER did not confer neutralization breadth to heterologous virus. These results suggest that strain-specific Abs target areas distinct from those targeted by cross-neutralizing Abs. Gray *et al.* [2007] (**antibody interactions, autologous responses, neutralization, variant cross-recognition or cross-neutralization, acute/early infection**)

No. 1076

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**References** Haim *et al.* 2007

**Keywords** kinetics, neutralization, variant cross-recognition or cross-neutralization



- Controlled attachment of Ab-bound HIV to cells was not affected by the presence of HIVIG. However, the virus was still efficiently neutralized indicating that binding of IgG to the cell-free virus interferes with a step of infection subsequent to cell attachment. Compared to b12, the neutralizing effect of IgG was sustained over extended time frames during the viral entry phase, significantly beyond the stage of CD4 engagement. Haim *et al.* [2007] (**neutralization, variant cross-recognition or cross-neutralization, kinetics**)

No. 1077

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Subtype** B, C

**Neutralizing**

**Immunogen** HIV-1 infection, vaccine

*HIV component:* mimotopes

**Species (Isotype)** human (IgG)

**References** Humbert *et al.* 2007

**Keywords** antibody generation, mimotopes, neutralization, rate of progression, vaccine antigen design, variant cross-recognition or cross-neutralization

- This study showed a significantly higher neutralizing Ab activity against a panel of HIV-1 isolates in LTNP than in progressors. Random peptide phage libraries were screened with plasma IgGs from the LTNP and 700 HIV-specific mimotopes were sequenced and analyzed for their capacity to represent conformational epitopes on the surface of gp120 using 3DEX software. Related phage groups were shown to be cross-reactive with the LTNP plasma. Immunization of mice with pools of mimotopes resulted in sera neutralizing various HIV-1 strains (D117III, JR-CSF and MH08). Humbert *et al.* [2007] (**antibody generation, mimotopes, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization, rate of progression**)

No. 1078

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env (SHIV SF162P4)

**Epitope**

**Subtype** B

**Neutralizing** L, P

**Immunogen** SHIV infection

**Species (Isotype)** macaque

**References** Kraft *et al.* 2007

**Keywords** acute/early infection, escape, neutralization, variant cross-recognition or cross-neutralization

- This study tracked neutralizing antibody development in a rhesus macaques. Homologous NABs were developed in the majority of the animals within the first month of infection while heterologous NAB responses developed over time only in animals with sustained plasma viremia. Viral replication persisted in these animals due to viral escape, and complex quasispecies developed over two years with mutations distributed over the envelope protein. Breadth of NAB

responses was as great in two years in the macaques as is seen in HIV infected patients over 10 years. Kraft *et al.* [2007] (**neutralization, variant cross-recognition or cross-neutralization, acute/early infection, escape**)

No. 1079

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp140

**Epitope**

**Subtype** A, B, C, M

**Neutralizing** P

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade JRFL, Other, B clade BaL, A clade 92RW020, C clade 97ZA012, M group Consensus *HIV component:* gp120, gp140ΔCFI, Other *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** guinea pig

**References** Liao *et al.* 2006

**Keywords** antibody binding site definition and exposure, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- A group M consensus envelope gene (CON-S) was designed that was central to the M group and a consensus of the consensus sequences of the major clades. The gp140δCFI protein of this virus and gp140CFI and gp140CF proteins of CON6 and other WT viruses were expressed in recombinant vaccinia viruses. The CON-S was shown to induce cross-subtype neutralizing Abs in immunized guinea pigs with greater breadth (neutralizing most A, B and C clade isolates) and titer than the WT proteins. Much of the neutralizing activity induced by CON-S Env was absorbed by the CON-S V3 peptide. Liao *et al.* [2006] (**antibody binding site definition and exposure, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1080

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (MN)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade MN *HIV component:* V3 *Adjuvant:* Cholera toxin (CT)

**Species (Isotype)** mouse (IgA, IgG, IgG1, IgG2a)

**Ab Type** gp120 V3-C4

**References** Varona-Santos *et al.* 2006

**Keywords** adjuvant comparison, genital and mucosal immunity, mucosal immunity, vaccine antigen design

- Mice were immunized intramuscularly and intranasally with a synthetic C4V3 peptide carrying three HIV-1 gp120 epitopes. It was shown that this peptide could efficiently be produced in *E. coli* and also induce strong systemic and mucosal anti-HIV-1 specific immune responses in mice. The responses

were induced without adjuvant, CT was shown to stimulate mucosal immune responses only when applied with low doses of the protein. Varona-Santos *et al.* [2006] (**adjuvant comparison, genital and mucosal immunity, vaccine antigen design, mucosal immunity**)

**No.** 1081  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with protein boost  
*HIV component:* Other *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** rabbit, mouse  
**References** Law *et al.* 2007  
**Keywords** neutralization, vaccine antigen design

- High levels of gp120-specific Abs were elicited when mice and rabbits were immunized by DNA priming and protein boosting with G1 and G2 grafts, consisting of 2F5 and 4E10, and 4E10 epitopes, respectively, engrafted into the V1/V2 region of gp120. A consistent NAb response against the homologous JR-FL virus was detected in rabbits but not in mice. 4E10 bound to the engrafted construct, but embedding the MPER epitopes in the immunogenic V1/V2 region did not result in eliciting anti-MPER antibodies in mice or rabbits. Law *et al.* [2007] (**neutralization, vaccine antigen design**)

**No.** 1082  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with protein boost  
*Strain:* B clade *HIV component:* gp140, gp160 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)  
**Species (Isotype)** rabbit (IgG)  
**References** Reynard *et al.* 2007  
**Keywords** acute/early infection, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- The potential of HIV-1 acute infection Env glycomutants designed from 3D model to elicit neutralizing responses in rabbits was evaluated. Specific potential N-linked glycosylation sites were removed that rendered an Env more neutralization susceptible; these forms were then tested as immunogens in rabbits. It was shown that the protein boosts induced a strong Env-specific antibody response mainly directed against conformational epitopes. The Ab avidity increased constantly through the immunizations. For one glycomutant, the neutralization breadth was increased compared to WT. The WT used as the basis for this study was isolated from a homosexual individual with acute B clade infection. Reynard

*et al.* [2007] (**neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization, acute/early infection**)

**No.** 1083  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Subtype** C, G  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Rong *et al.* 2007  
**Keywords** escape, neutralization

- Resistance to NAb in plasma from resistant donor-sensitive recipient pairs was correlated with sequence divergence in the gp120 V1-V4 region and to acquisition of length in the gp120 hypervariable domains in donor plasma. Association between nine amino acid positions in V1-V4 and Ab resistance was found, where five of the positions were located in the alpha-2 helix of the gp120 outer domain. These same 5 positions were found to be under positive selection pressure in subtype C sequences from Los Alamos Sequence Database. However, exchange of the alpha-2 helix between resistant donor and sensitive recipient Envs did not alter NAb phenotype, suggesting that positions within alpha-2 helix must be linked to other domains of Env to utilize NAb escape. Rong *et al.* [2007] (**neutralization, escape**)

**No.** 1084  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade MN, B clade RF, Other *HIV component:* V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)  
**Species (Isotype)** mouse  
**Ab Type** gp120 V3  
**References** Eda *et al.* 2006b  
**Keywords** antibody generation, neutralization, variant cross-recognition or cross-neutralization

- Sequential immunizations of mice with V3 peptides from clade B isolates resulted in an Ab response capable of neutralizing homo- and heterologous forms of the CXCR4-tropic HIV-1 MN and CCR5-tropic HIV-1 JR-CSF. In contrast, repeated immunizations with a single V3 peptide resulted in Ab response that neutralized only type-specific laboratory-adapted homologous viruses. A novel cross-reactive Ab was isolated and humanized, KD-247. Eda *et al.* [2006b] (**antibody generation, neutralization, variant cross-recognition or cross-neutralization**)

**No.** 1085  
**MAb ID** polyclonal

**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Subtype** B, C  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Li *et al.* 2006a  
**Keywords** acute/early infection, autologous responses, neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- This study examined the course and magnitude of autologous neutralizing Ab response during early HIV-1 infection in patients infected with subtypes B and C. It was found that subtype C infected individuals had a 3.5-fold higher IC50-titers of NABs in plasma than subtype B infected individuals. The higher NAB titers were associated with the significantly shorter length of the HIV-1 V1-V4 regions of subtype C virus. However, despite the potency of the subtype C NAB response, the response was not found to be directed against the cross-neutralizing epitopes. The intrasubtype cross-neutralizing activity was much more prevalent in subtype B HIV-1. This indicates existence of clade-specific differences of Env-associated immunogenicity or neutralization susceptibility. Li *et al.* [2006a] (**autologous responses, neutralization, variant cross-recognition or cross-neutralization, acute/early infection, subtype comparisons**)

**No.** 1086  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with protein boost  
*Strain:* B clade YU2 *HIV component:* gp120, gp140 *Adjuvant:* C3d fusion, Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** mouse (IgG, IgG1, IgG2a, IgG2b, IgG3)  
**References** Bower *et al.* 2006  
**Keywords** binding affinity, neutralization, vaccine antigen design

- Mice were vaccinated with high or low dose DNA plasmids expressing Envgp120, Envgp120-mC3d, Envgp140, or Envgp40-mC3d, and boosted with trimeric Envgp140. Mice vaccinated with high dose DNA followed by trimer Envgp140 boost developed highest anti-Env titers and the broadest number of IgG isotypes. However, Envgp140 trimers did not appear to elicit higher titers of Abs that recognized conformational Env epitopes compared to Envgp120 monomers. Mice vaccinated with C3d fused envelopes had Abs with highest avidity, and Envgp140-mC3d was shown to elicit slightly higher neutralization titers for ADA and YU-2 isoaltes than Envgp120. These results indicate that although gp140 trimers are slightly more efficient at eliciting NAB than gp120, the neutralizing ability does not correlate with the induction of conformational antibodies. Bower *et al.* [2006] (**neutralization, vaccine antigen design, binding affinity**)

**No.** 1087  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* vesicular stomatitis virus (VSV) *Strain:* B clade HXB2 *HIV component:* gp120  
**Species (Isotype)** mouse  
**References** Jiang *et al.* 2006  
**Keywords** neutralization, vaccine antigen design

- Mice immunized intranasally with VSV vector expressing HIV-1 HXB2 gp120 developed anti-HIV-1 response. Mouse sera was shown to be able to neutralize HXB2 and JRFL envelope-pseudotyped viruses. Jiang *et al.* [2006] (**neutralization, vaccine antigen design**)

**No.** 1088  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Cham *et al.* 2006  
**Keywords** neutralization, subtype comparisons, variant cross-recognition or cross-neutralization

- Neutralization properties of viruses pseudotyped with Envs derived from individuals with broadly cross-reactive HIV-1 neutralizing sera (BCN) and individuals without BCN sera were examined. All the primary Env-pseudotyped viruses were neutralized by BCN sera while non-BCN sera all failed to neutralize one or more strains tested. The overall geometric mean titers of the BCN sera were higher than those of non-BCN sera. BCN and non-BCN pseudotyped viruses showed similar sensitivity to neutralization by anti-gp120 MAbs while the BCN pseudotyped viruses tended to be more sensitive to the anti-gp41 MAbs. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 1089  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA, peptide *Strain:* A clade, B clade, B clade IIIB, B clade LAI, Other *HIV component:* gp160, mimotopes, Rev *Adjuvant:* cationic liposome  
**Species (Isotype)** mouse (IgA, IgG)  
**References** Hinkula *et al.* 2006  
**Keywords** adjuvant comparison, genital and mucosal immunity, mucosal immunity, neutralization, subtype comparisons, vaccine antigen design

- Mice were immunized with rgp160 DNA-prime and Rev gp41 boost and a novel cationic lipid DNA (N3) was evaluated as adjuvant. It was shown that in the presence of N3 adjuvant, 10-fold less DNA was needed in the immunization to obtain serum IgG and IgA response. gp41 peptide boost in L3 adjuvant increased serum IgG and IgA titers against HIV-1 envelope and clade A, B and C peptides. In addition, the boost resulted in detectable levels of gp160-specific IgA mucosal responses. Immunized mouse serum neutralized clade A, B and C HIV-1 strains. Hinkula *et al.* [2006] (**adjuvant comparison, genital and mucosal immunity, neutralization, vaccine antigen design, mucosal immunity, subtype comparisons**)

No. 1090

MAB ID polyclonal

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing

Immunogen vaccine

*Vector/Type:* peptide *Strain:* B clade  
*HIV component:* V3 *Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

Species (Isotype) guinea pig (IgG)

Ab Type gp120 V3

References Haynes *et al.* 2006

**Keywords** antibody generation, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 29 subtype B V3 peptides were designed and used for immunization of guinea pigs. The most effective peptide was of subtype B consensus sequence and induced Abs that neutralized 31% subtype B isolates but had limited cross-neutralization activity to non-B strains. This study suggests that the neutralizing breadth obtained with selected V3 immunogens is limited. Haynes *et al.* [2006] (**antibody generation, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1091

MAB ID polyclonal

HXB2 Location Env

Author Location

Epitope

Neutralizing

Immunogen vaccine

*Vector/Type:* protein *Strain:* B clade BaL  
*HIV component:* gp120 *Adjuvant:* trehalose dicorynomycolate

Species (Isotype) mouse

References Abdel-Motal *et al.* 2006

**Keywords** neutralization, vaccine antigen design

- The immunogenicity of gp120 was increased by replacing its multiple sialic acid residues on the carbohydrate chains by alpha-gal epitopes. These epitopes are recognized by the anti-Gal Ab that targets the Ab-gp120 complexes to APC, thereby increasing the uptake of gp120 by APCs. Production of anti-gp120 Abs in mice immunized with the recombinant gp120 was 100-fold higher than the production of anti-gp120 Ab

in mice immunized with gp120. Anti-gp120 Abs from mice immunized with the recombinant gp120 effectively neutralized HIV-1 lab strain MN while no neutralization activity was observed for Abs from mice immunized with gp120. Abdel-Motal *et al.* [2006] (**neutralization, vaccine antigen design**)

No. 1092

MAB ID polyclonal

HXB2 Location Env

Author Location gp120

Epitope

Subtype A, B, C, CRF01\_AE

Neutralizing

Immunogen vaccine

*Vector/Type:* Other *Strain:* B clade MN, B clade SF162 *HIV component:* Env, gp140ΔV2, Rev *Adjuvant:* MF59

Species (Isotype) chimpanzee

References Gómez-Román *et al.* 2006

**Keywords** ADCC, neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- Chimpanzees were immunized with Ad5- and Ad7-HIVenv/rev recombinant prime and gp140deltaV2 protein boost in MF59 adjuvant. The vaccine induced high titers of subtype A, B, C and CRF01\_AE gp120-binding Abs. Most of the sera cross-neutralized a heterologous subtype C isolate but not other A, C and CRF01\_AE isolates. The vaccine also elicited cross-clade ADCC activity against subtypes A, B, C and CRF01\_AE in the majority of sera. Gómez-Román *et al.* [2006] (**ADCC, neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1093

MAB ID polyclonal

HXB2 Location Env

Author Location Env

Epitope

Subtype B

Neutralizing P

Immunogen HIV-1 infection

Species (Isotype) human

References Davis *et al.* 2006

**Keywords** kinetics, neutralization, variant cross-recognition or cross-neutralization

- Neutralization kinetics for sensitive and resistant HIV-1 clade B primary isolates were determined. The neutralization assays were varied for the time of the phase where the virus reacts with the Abs and the subsequent phase where virus-Ab is exposed to target cells. The minority of combinations showed exponentially falling titers as long as the free virions were exposed to Ab. The majority of combinations showed deviations that may be attributed to events after the virion-Ab mixture is added to target cells: significant neutralization with minimal exposure of the free virions to Ab. The neutralization of either free virion or cell-associated virus did not correlate with the resistance/sensitivity properties of primary subtype B isolates. Davis *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, kinetics**)

**No.** 1094  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**References** Huber *et al.* 2006  
**Keywords** acute/early infection, complement, neutralization, variant cross-recognition or cross-neutralization

- Complement induced lysis activity against autologous virus and a heterologous primary isolate, HIV-1 JR-FL, was shown to be higher in patients in the chronic stage of infection than in patients in the acute stage. However, plasma viral loads during the acute stage of infection were inversely correlated with the autologous complement lysis activity, suggesting that the antibody-mediated virion lysis is effective early in the course of infection. Titers of Abs to gp120 and gp41 increased with increased lysis activity, indicating that early anti-Env responses mediate complement lysis. No association between neutralization and complement lysis activity was observed, suggesting that complement lysis is predominantly caused by non-neutralizing Abs. Huber *et al.* [2006] (**complement, neutralization, variant cross-recognition or cross-neutralization, acute/early infection**)

**No.** 1095  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing**  
**Immunogen** SHIV infection, vaccine  
*Vector/Type:* DNA prime with protein boost  
*Strain:* B clade SF162 *HIV component:* gp140, gp140ΔV2, Other *Adjuvant:* MF59  
**Species (Isotype)** macaque  
**References** Burke *et al.* 2006  
**Keywords** neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization

- Macaques were immunized with three different SF162 Env-based gp140 immunogens and challenged simultaneously with the homologous SHIV(SF162P4) and heterologous SHIV(SF33A) viruses. The immunization did not protect against infection as all animals were dually infected but it did reduce the viral replication of the homologous virus during primary infection. The immunization elicited neutralizing Ab against the homologous SF162P4 virus. Sera from animals immunized with two of the gp140 immunogens also neutralized heterologous 89.6 and HXB2 viruses while all other heterologous viruses were resistant to neutralization. Burke *et al.* [2006] (**neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization**)

**No.** 1096  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env

**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA, DNA prime with protein boost *Strain:* B clade 89.6, B clade HXB2 *HIV component:* gp140ΔCFI *Adjuvant:* Incomplete Freund's Adjuvant (IFA), IL-15, Other  
**Species (Isotype)** rabbit, mouse (IgG, IgG1, IgG2a, IgG2b, IgG3, IgM, IgG2)  
**References** Bolesta *et al.* 2006  
**Keywords** ADCC, complement, neutralization, vaccine antigen design

- Rabbits immunized with HXB2 derived gp140deltaCFI plasmid DNA with the most divergent region replaced with the corresponding sequence of 89.6 Env, and boosted with gp140deltaCFI protein developed Ab responses. The Ab neutralizing activity was detected against homologous 89.6 virus while other HIV-1 isolates were neutralized less effectively. Mice immunized with the gp140deltaCFI construct developed IgM responses with no effect of the presence or absence of IL-15 and IL-21 in the immunization assay. In contrast, coimmunization with IL-15 and IL-21 augmented Env-specific IgG responses, where IL-15 augmented IgG2a and IgG2b responses and IL-21 augmented Env-specific IgG1 Abs. None of the cytokines affected IgG3 Ab responses. The use of IL-15 and IL-21 was also shown to increase Ab-dependent cellular cytotoxicity and complement-dependent lysis of Env-expressing target cells. Bolesta *et al.* [2006] (**ADCC, complement, neutralization, vaccine antigen design**)

**No.** 1097  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade *HIV component:* gp120 *Adjuvant:* monophosphoryl lipid A  
**Species (Isotype)** hamster (IgG)  
**References** Azizi *et al.* 2006  
**Keywords** neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- Three groups of hamsters were immunized with gp120 protein cloned from subtype B infected individuals, where group 1 received gp120 from one patient, group 2 from 4 patients and group 3 from all 14 patients. Group 3 (polyvalent vaccine) plasma showed higher IgG Ab titer to HIV-1 subtype B isolates MN and SF162 than the other groups, but not to subtypes C and A/E. The polyvalent vaccine showed similar neutralizing activity against the MN strain as the 4-protein group. All vaccines failed to neutralize other primary HIV-1 isolates. Azizi *et al.* [2006] (**neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 1098  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Braibant *et al.* 2006  
**Keywords** neutralization, rate of progression, subtype comparisons, variant cross-recognition or cross-neutralization

- Sera from HIV-1 infected long-term non-progressors were tested for neutralization activity against four heterologous primary isolates. 16% of the sera showed broadly neutralizing activity against the four strains. Cross-clade neutralization was detected in some cases but subtype-specific neutralization predominated. Braibant *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons, rate of progression**)

**No.** 1099  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** C  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Gray *et al.* 2006  
**Keywords** mother-to-infant transmission, neutralization, responses in children, variant cross-recognition or cross-neutralization

- Env-pseudotyped viruses were constructed from the gp160 envelope genes from seven children infected with subtype C HIV-1. All pseudoviruses except one were neutralized by one or both of the plasma samples tested. Gray *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, responses in children, mother-to-infant transmission**)

**No.** 1100  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *Adjuvant:* gp41 N-HR and C-HR helical peptides  
**Species (Isotype)** rabbit (IgG)  
**Ab Type** C-HR, N-HR, gp41six-helix bundle  
**References** Golding *et al.* 2002b; de Rosny *et al.* 2001

- The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter anti-C-HR Abs inability to inhibit fusion. Golding *et al.* [2002b]
- A panel of Abs against gp41 heptad repeats N-HR, C-HR, and self-assembled stable N-HR and C-HR six helix bundles were generated. de Rosny *et al.* [2001]

**No.** 1101  
**MAb ID** 101-342  
**HXB2 Location** Env  
**Author Location** gp120 (476–505 HAM112, O group)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* O group HAM112 *HIV component:* gp160  
**Species (Isotype)** mouse (IgG2ak)  
**Ab Type** C-term  
**References** Scheffel *et al.* 1999

- 101-342: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity. Scheffel *et al.* [1999]

**No.** 1102  
**MAb ID** 101-451  
**HXB2 Location** Env  
**Author Location** gp120 (498–527 HAM112, O group)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* O group HAM112 *HIV component:* gp160  
**Species (Isotype)** mouse (IgG2bk)  
**Ab Type** C-term  
**References** Scheffel *et al.* 1999

- 101-451: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity. Scheffel *et al.* [1999]

**No.** 1103  
**MAb ID** 120-1  
**HXB2 Location** Env  
**Author Location** gp120 (503–532)  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* peptide  
**Species (Isotype)** mouse (IgMκ)  
**Ab Type** C-term  
**References** Dalgleish *et al.* 1988; Chanh *et al.* 1986

**No.** 1104  
**MAb ID** T26  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing**

**Immunogen** vaccine  
*Vector/Type:* protein  
**Species (Isotype)** mouse  
**Ab Type** C-term  
**Research Contact** Patricia Earl, National Institute of Allergy and Infectious Diseases  
**References** Kilgore *et al.* 2003; Earl *et al.* 1997; Earl *et al.* 1994  
**Keywords** antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization

- T26: Mab is restricted in its binding to gp41 of the LAI isolate and not to gp41 of the MN, Ada and RF isolates. Antibody specificity may be determined by LAI residues D637E, N641D and H648Y. T26 binds to the N-terminal half of the C helix (aa630-680) of the LAI envelope, specifically targeting a conformational epitope within the six-helix bundle of gp41. Addition of the C-helical peptide inhibitor from LAI (T26 reactive) rescued the binding activity of MAb T26 to cell-surface expressed RF envelope (T26 non-reactive) triggered with sCD4 or cell-surface expressed receptors in a surface immunoprecipitation assay. This supports that C-peptide entry inhibitors bind to the gp41 N-helical coiled-coil, disrupting native six-helix bundles. Kilgore *et al.* [2003] (**antibody binding site definition and exposure**)
- T26: T26 was raised against the gp140 tetramer, binds to gp41 and is a highly strain specific. Earl *et al.* [1997] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- T26: A panel of 138 MAb raised against different forms of soluble Env. Earl *et al.* [1994] (**antibody generation**)

**No.** 1105  
**MAb ID** D33  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 CD4BS, C-term, N-term  
**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD  
**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D33: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D33 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4 – D33 was unusual for the group of A1 MAbs, because while it blocked CD4 binding completely, but competed with MAbs that did not in a BIA-core assay – both the N- and C-terminal ends of gp120 are involved in D33 binding. Sugiura *et al.* [1999]
- D33: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1106  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgA)  
**Ab Type** gp120 CD4BS, C-term, gp120 V3-C4  
**References** Vincent *et al.* 2004  
**Keywords** genital and mucosal immunity

- IgA derived from sera and saliva from 5 HIV-1 infected patients undergoing ART therapy reacted to peptide antigens corresponding to the C3-V4 region of gp120 and the C-terminal part of gp41. HIV-1-specific IgA obtained in 6/26 sera and 5/25 saliva samples inhibited gp120-sCD4 protein binding. Vincent *et al.* [2004] (**genital and mucosal immunity**)

**No.** 1107  
**MAb ID** 212A  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 C1  
**Research Contact** James Robinson, Tulane University, LA  
**References** Pantophlet *et al.* 2004; Pantophlet *et al.* 2003b; Binley *et al.* 1998; Sullivan *et al.* 1998b; Parren *et al.* 1997b; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Moore & Sodroski 1996; Moore *et al.* 1994d; Robinson *et al.* 1992

**Keywords** vaccine antigen design

- 212A: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 212A. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 212A: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 212A: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]

- 212A: Does not compete with binding of MAb generated in response to gp120-CD4 complex, CG10. Sullivan *et al.* [1998b]
- 212A: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 212A bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997]
- 212A: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b]
- 212A: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids are deleted. Wyatt *et al.* [1997]
- 212A: Binding enhanced by anti-V3 MAb 5G11 – reciprocal inhibition with anti-C1 MAbs. Moore & Sodroski [1996]
- 212A: Mutations that inhibit binding: C1 (45 W/S) and V5 (463 N/D) – and enhance binding: V2 (179/180 LD/DL) and C5 (495 G/K). Moore *et al.* [1994d]

No. 1108

MAb ID 522-149

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing no

Immunogen vaccine

Vector/Type: protein HIV component: Env

Species (Isotype) mouse

Ab Type gp120 C1

Research Contact G. Robey, Abbott Inc.

References Pantophlet *et al.* 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Yang *et al.* 2000; Binley *et al.* 1998; Trkola *et al.* 1996a; Moore & Sodroski 1996

Keywords antibody interactions, vaccine antigen design

- 522-149: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 522-149. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 522-149: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 522-149: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope

spike, and IgG1b12 can uniquely remain unaffected. This is a C1-binding Fab that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)

- 522-149: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- 522-149: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 522-149: Binding is enhanced by C5 antibodies M91 and 1C1 – mutual binding-inhibition with anti-C1 antibody 133/290 – binding is destroyed by a W/L (position 61, LAI) gp120 amino acid substitution – other C1 antibodies enhance binding to gp120. Moore & Sodroski [1996]
- 522-149: Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]

No. 1109

MAb ID CA1 (ARP3117)

HXB2 Location Env

Author Location Env

Epitope

Subtype A

Neutralizing

Immunogen vaccine

Vector/Type: vaccinia prime with gp120 boost Strain: A clade HIV component: Env

Species (Isotype) mouse

Ab Type gp120 C1

References Jeffs *et al.* 2004

Keywords subtype comparisons, vaccine antigen design

- CA1: A set of oligomeric envelope proteins were made from six primary isolates for potential use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. CA1 is a MAb that binds to a linear epitope in the C1 region of gp120 that was raised against clade A variant 92/UG/029. CA1 was subtype-specific and bound only to the antigen from all clade A. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design, subtype comparisons**)



**No.** 1110  
**MAb ID** L19  
**HXB2 Location** Env  
**Author Location** gp120 (HXBc2)  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1)  
**Ab Type** gp120 C1  
**References** Ditzel *et al.* 1997

- L19: gp120 immobilized on solid phase by capture with anti-CD4 BS MAb L72 was used for the selection of Fabs – six N-term Fabs, L19 L34, L35, L52, L59, and L69, were obtained that have a similar epitope to Fab p7. Ditzel *et al.* [1997]

**No.** 1111  
**MAb ID** M90  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Env  
**Species (Isotype)** (IgG1)  
**Ab Type** gp120 C1  
**Research Contact** Fulvia di Marzo Veronese  
**References** Koefoed *et al.* 2005; Pantophlet *et al.* 2003b; Yang *et al.* 2000; Binley *et al.* 1999; Binley *et al.* 1998; Wyatt *et al.* 1997; Ditzel *et al.* 1997; Moore & Sodroski 1996; DeVico *et al.* 1995; di Marzo Veronese *et al.* 1992

**Keywords** antibody binding site definition and exposure

- M90: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. M90 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, and has a conformational C1 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- M90: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b]
- M90: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]

- M90: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAb IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]
- M90: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- M90: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-82, are deleted. Wyatt *et al.* [1997]
- M90: Reciprocal inhibition of binding of other anti-C1 MAbs – inhibits CD4 binding site MAbs – enhances binding of V2 MAbs G3-4 and SC258. Moore & Sodroski [1996]
- M90: Reacted with both non-reduced (but not denatured) covalently cross-linked gp120-CD4 complex. DeVico *et al.* [1995]
- M90: Reactive only with native gp120, so binds to a discontinuous epitope – reacts with multiple strains. di Marzo Veronese *et al.* [1992]

**No.** 1112  
**MAb ID** MAG 104  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 C1  
**Research Contact** C. Y. Kang, IDEC Inc  
**References** Kang *et al.* 1994

- MAG 104: Only observed amino acid substitution that reduces binding: 88 N/P and 106 E/A – does not bind to C1 region 20 mer peptides, tentative classification conformationally sensitive anti-C1 MAb. Kang *et al.* [1994]

**No.** 1113  
**MAb ID** MAG 45 (#45, MAG45)  
**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* sCD4-gp120 complex *Strain:*  
B clade HXB2 *HIV component:* gp120

**Species (Isotype)** mouse

**Ab Type** gp120 C1

**Research Contact** C. Y. Kang, IDEC Inc, or Dr. Hariharam, IDEC Pharmaceuticals Corporation, La Jolla, CA

**References** Koefoed *et al.* 2005; Yang *et al.* 2000; Wyatt *et al.* 1997; Moore & Sodroski 1996; Kang *et al.* 1994

**Keywords** antibody binding site definition and exposure

- MAG 45: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. MAG 45 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MABs, representing a MAB with a C1 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- MAG 45: Called #45 – a combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MABs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MABs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MABs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- MAG 45: Called #45 – binds to efficiently sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-50, are deleted. Wyatt *et al.* [1997]
- MAG 45: Reciprocal binding inhibition with anti-C1-C5 and anti-C1-C4 discontinuous MABs – binding enhanced by anti-V3 5G11 – inhibits binding of anti-CD4 binding site MABs. Moore & Sodroski [1996]
- MAG 45: Only observed amino acid substitution that reduces binding: 88 N/P – does not bind to C1 region 20 mer peptides, tentative classification conformationally sensitive anti-C1 MAB. Kang *et al.* [1994]

**No.** 1114

**MAB ID** MAG 95

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* sCD4-gp120 complex *Strain:*  
B clade HXB2 *HIV component:* gp120

**Species (Isotype)** mouse

**Ab Type** gp120 C1

**Research Contact** C. Y. Kang, IDEC Inc

**References** Kang *et al.* 1994

- MAG 95: Only observed amino acid substitution that reduces binding: 88 N/P – does not bind to C1 region 20 mer peptides, tentative classification conformationally sensitive anti-C1 MAB. Kang *et al.* [1994]

**No.** 1115

**MAB ID** MAG 97

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* sCD4-gp120 complex *Strain:*  
B clade HXB2 *HIV component:* gp120

**Species (Isotype)** mouse

**Ab Type** gp120 C1

**Research Contact** C. Y. Kang, IDEC Inc

**References** Kang *et al.* 1994

- MAG 97: Only observed amino acid substitution that reduces binding: 88 N/P – does not bind to C1 region 20 mer peptides, tentative classification conformationally sensitive anti-C1 MAB. Kang *et al.* [1994]

**No.** 1116

**MAB ID** P35

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 C1

**References** Zwick *et al.* 2003; Kwong *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody interactions

- P35: called p35. scFv 4KG5 reacts with a conformational epitope. Of a panel of MABs tested, only NAB b12 enhanced 4KG5 binding to gp120. MABs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MABs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restrict CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C1-binding Fab with a discontinuous epitope that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- P35: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAB ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MABs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAB b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MABs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MABs

that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the epitope as N-terminal, linear. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)

No. 1117

**MAb ID** T9

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*HIV component: oligomeric gp140*

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 C1

**Research Contact** Patricia Earl and Christopher Broder, NIH

**References** Golding *et al.* 2002b; Earl *et al.* 1997; Broder *et al.* 1994

**Keywords** antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization

- T9 database comment: There are two HIV-Abs with the name T9, one binds to gp41, one to gp120.
- T9: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b – nor did it alter two gp41 MAbs, T9 and D61, inability to inhibit fusion. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)
- T9: This antibody, along with 7 others (M10, D41, D54, T6, T4, T10 and T35), can block the linear murine MAb D61, and the human MAb 246-D, which both bind to the immunodominant region near the two Cys in gp41 – most of these antibodies are oligomer dependent – all of the MAbs are reactive with ten different HIV-1 strains – members of this competition group are blocked by sera from HIV-1 + individuals. Earl *et al.* [1997] (**antibody binding site definition and exposure**)
- T9: One of five MAbs (T4, T6, T9, T10 and T35) in a competition group that bind to a conformation-dependent epitope in gp41 and is oligomer specific – neutralizes IIIB and SF2. Broder *et al.* [1994] (**antibody generation, variant cross-recognition or cross-neutralization**)

No. 1118

**MAb ID** p7

**HXB2 Location** Env

**Author Location** gp120 (HXBc2)

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1)

**Ab Type** gp120 C1

**References** Parren *et al.* 1997b; Ditzel *et al.* 1997

- p7: gp120 immobilized on solid phase by capture with sCD4 was used for selection of Fabs – three novel N-term Fabs were obtained that bind to similar epitopes, p7, p20, and p35 – a C1 W/S substitution at position 45 abolished binding, a Y/D at position 45 reduced binding, and C5 region substitutions 475 M/S and 493 P/K enhanced binding – compete with MAbs M85, M90 and 212A, but not M91 and G3-299. Ditzel *et al.* [1997]
- p7: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b]

No. 1119

**MAb ID** L100

**HXB2 Location** Env

**Author Location** gp120 (HXBc2)

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1)

**Ab Type** gp120 C1-C2

**References** Kwong *et al.* 2002; Parren & Burton 1997; Parren *et al.* 1997b; Ditzel *et al.* 1997

**Keywords** antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization

- L100: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the epitope as N-terminal, discontinuous. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- L100: gp120 immobilized on solid phase by capture with sCD4 and then masked with Fab p7 allowed selection of a new Fab, L100, with a novel specificity for C1 and C2 – gp120 C1 substitutions 69 W/L and 76 P/Y abolish L100 binding, and C2 substitutions 252 R/W, 256 S/Y, 262 N/T and 267 E/L abolish or strongly inhibit L100 binding – inhibits binding of

MAbs M90 and G3-299, but not M85, 212A, and M91. Ditzel *et al.* [1997]; Parren & Burton [1997] (**antibody binding site definition and exposure, antibody generation**)

- L100: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

No. 1120

**MAB ID** 2/11c (211c, 2.11c, 211/c, 2-11c)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L (weak)

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 C1-C4

**Research Contact** James Robinson, Tulane University, LA

**References** Kwong *et al.* 2002; Xiang *et al.* 2002a; Binley *et al.* 1998; Wyatt *et al.* 1997; Li *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Trkola *et al.* 1996a; Moore & Sodroski 1996

**Keywords** antibody binding site definition and exposure

- 2/11c: Called 211/c. Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the epitope as N-terminus, discontinuous. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- 2/11c: Used as a negative control in a study of CD4i MAbs. Xiang *et al.* [2002a]
- 2/11c: Called 211/c – a panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998]
- 2/11c: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric env binding – 2/11c bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997]

- 2/11c: Called 2.11c – One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – 50% neutralization could not be achieved at a maximal concentration of 67 µg/ml. Li *et al.* [1997]
- 2/11c: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-74, are deleted. Wyatt *et al.* [1997]
- 2/11c: Inhibits binding of anti-C1, -C5, -C4, -V3 and anti-CD4 binding site MAbs – induces binding of some anti-V2 and CD4i MAbs (48d and 17b) – similar reactivity pattern to A32, but less cross-reactive and lower affinity – A32 and 211/c are unique among known human and rodent MAbs. Moore & Sodroski [1996]
- 2/11c: Called 211c – does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]

No. 1121

**MAB ID** A32

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1)

**Ab Type** gp120 C1-C4, gp120 adjacent to CD4BS

**Research Contact** James Robinson, Tulane University, New Orleans, LA, USA

**References** Liao *et al.* 2006; Haynes & Montefiori 2006; Selvarajah *et al.* 2005; Haynes *et al.* 2005; Pantophlet *et al.* 2004; Liao *et al.* 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Kwong *et al.* 2002; Grundner *et al.* 2002; Yang *et al.* 2002; Finnegan *et al.* 2001; Yang *et al.* 2000; Binley *et al.* 1999; Binley *et al.* 1998; Sullivan *et al.* 1998b; Parren *et al.* 1997b; Boots *et al.* 1997; Wyatt *et al.* 1997; Burton & Montefiori 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Trkola *et al.* 1996a; Wu *et al.* 1996; Moore & Sodroski 1996; Moore & Ho 1995; Wyatt *et al.* 1995; Moore *et al.* 1994b

**Keywords** antibody binding site definition and exposure, antibody interactions, co-receptor, enhancing activity, mimotopes, review, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- A32: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure, enhancing activity**)

- A32: The gp140 $\delta$ CFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. A32 was shown to bind specifically to all recombinant proteins except for the one derived from subtype C virus. It also bound specifically to the two subtype B gp120 proteins. The specific binding of A32 to CON-S indicated that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure, vaccine antigen design, subtype comparisons**)
- A32: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)
- A32: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V1/V2/V3 MAb 4KG2, C1-C4 MAb A32, C1-C5 MAb C11, and HIVIG all either did not bind or had significantly diminished binding to both antigen constructs. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- A32: A32-rgp120 complexes opened up the CCR5 co-receptor binding site, but did not induce neutralizing antibodies with greater breadth among B subtype isolates than did uncomplexed rgp120 in vaccinated guinea pigs. Liao *et al.* [2004] (**vaccine antigen design**)
- A32: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including A32. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- A32: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- A32: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. A32 is described as having a C1-C4 discontinuous CD4i epitope, and had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- A32: HIV-1 gp160 $\delta$ CT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines – 2F5 bound to gp160 $\delta$ CT with a reconstituted membrane ten-fold better than the same protein on beads – anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160 $\delta$ CT PLs indistinguishably from gp160 $\delta$ CT expressed on the cell surface – non-neutralizing MAbs C11 and A32 bound with lower affinity than NAb IgG1b12 – the MAb 17b was sCD4 inducible on gp160 $\delta$ CT PL. Grundner *et al.* [2002] (**vaccine antigen design**)
- A32: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Authors describe the epitope as N-terminal, discontinuous. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- A32: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibrin – stabilized oligomer gp140  $\delta$ 683(-FT) showed strong preferential recognition by NAb IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**antibody binding site definition and exposure**)
- A32: Using a cell-fusion system, it was found CD4i antibodies 17b, 48d, and CG10 reacted faintly with Env expressing HeLa cells even in the absence of sCD4 or CD4 expressing target cells. Reactivity increased after sCD4 addition, but not after CD4 expressing target cell addition, and binding was

not increased at the cell-to-cell CD4-Env interface. This suggests the CD4i co-receptor binding domain is largely blocked at the cell-fusion interface, and so CD4i antibodies would not be able access this site and neutralize cell-mediated viral entry. However, CD4i MAb 8F101 and A32, that bind outside the co-receptor domain, had a different pattern. They reacted after the formation of gp120-CD4-CXCR4 tri-complexes, so co-receptor interactions allowed exposure of their epitopes. Finnegan *et al.* [2001] (**antibody binding site definition and exposure**)

- A32: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000] (**vaccine antigen design**)
- A32: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAb IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**antibody binding site definition and exposure**)
- A32: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
- A32: Enhances binding of CD4i MAbs 17b and 48d, and a MAb generated in response to gp120-CD4 complex, CG10. Sullivan *et al.* [1998b] (**antibody interactions**)
- A32: Abs that recognize discontinuous epitopes can identify mimotopes from a phage peptide display library – A32 has a unique epitope involving mostly C2 but C1 and C4 contribute – six quite variable phage inserts were recognized, with a consensus of LPWYN – a central Trp was the most conserved element, consistent with W427 being an important residue for binding gp120. Boots *et al.* [1997] (**antibody binding site definition and exposure, mimotopes**)
- A32: Review. Burton & Montefiori [1997] (**review**)
- A32: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric env binding – A32 bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- A32: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- A32: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- A32: Reciprocal inhibition of binding of anti-C1, -C5, -C4, -V3 and anti-CD4 binding site MAbs – induces binding of some anti-V2 and sCD4 inducible MAbs (48d and 17b) – very similar competition pattern between 2/11c, A32 and 211/c are unique among known human and rodent MAbs. Moore & Sodroski [1996] (**antibody binding site definition and exposure, antibody interactions**)
- A32: Does not neutralize JR-FL, or any strain strongly – partial inhibition of gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**co-receptor**)
- A32: Not neutralizing – binds domains that interact with gp41 – MIP-1alpha binding to CCR-5 expressing cells can be inhibited by gp120-sCD4 and binding of A32 does not block this inhibition. Wu *et al.* [1996] (**antibody binding site definition and exposure**)
- A32: Review: epitope is distinct from CD4BS MAbs, 48d and 17b, and 2G12. Moore & Ho [1995] (**antibody binding site definition and exposure**)
- A32: Epitope is better exposed upon CD4 binding to gp120 – binding of A32 enhances binding of 48d and 17b – studies using a V1/V2 deletion mutant demonstrated that enhanced binding of 48d in the presence sCD4 involves the V1/V2 loops, with more significant involvement of V2. Wyatt *et al.* [1995] (**antibody binding site definition and exposure, antibody interactions**)
- A32: Reacted with virtually every gp120 monomer of every clade tested, most conserved gp120 monomer epitope known. Moore *et al.* [1994b] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1122

MAb ID C11 (c11)

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing no

Immunogen HIV-1 infection

Species (Isotype) human

Ab Type gp120 C1-C5

Research Contact James Robinson, Tulane University, LA

References Bowley *et al.* 2007; Selvarajah *et al.* 2005; Haynes *et al.* 2005; Pantophlet *et al.* 2004; Pantophlet *et al.* 2003b; Ohagen *et al.* 2003; Raja *et al.* 2003; Kwong *et al.* 2002; Basma-ciogullari *et al.* 2002; Grundner *et al.* 2002; Yang *et al.* 2002; Binley *et al.* 1999; Sullivan *et al.* 1998b; Parren *et al.* 1997b; Wyatt *et al.*

1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Wu *et al.* 1996; Trkola *et al.* 1996a; Moore & Sodroski 1996; Moore *et al.* 1994d; Robinson *et al.* 1992

- Keywords** antibody binding site definition and exposure, antibody interactions, assay standardization/improvement, brain/CSF, co-receptor, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization
- C11: Yeast display was compared to phage display and shown to select all the scFv identified by phage display and additional novel antibodies. Biotinylated C11 and 2G12 were used to minimize selection of non-gp120 specific clones from the yeast displayed antibody library; these MAbs were used as they have unique epitopes with limited overlap with most known epitopes. Bowley *et al.* [2007] (**assay standardization/improvement**)
  - C11: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. C11 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)
  - C11: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V1/V2/V3 MAb 4KG2, C1-C4 MAb A32, C1-C5 MAb C11, and HIVIG all either did not bind or had significantly diminished binding to both antigen constructs. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
  - C11: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including C11. Pantophlet *et al.* [2004] (**vaccine antigen design**)
  - C11: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. C11 recognized most variants, some from each of the four individuals, by gp120 immunoprecipitation. Ohagen *et al.* [2003] (**brain/CSF, variant cross-recognition or cross-neutralization**)
  - C11: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
  - C11: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. C11 was used as a negative control, as C11 binding did not alter binding of CD4-independent gp120 to CCR5, nor binding to CCR5-expressing Cf2Th cells. Raja *et al.* [2003] (**co-receptor**)
  - C11: gp120 mutants were used to define the CXCR4 binding site using CXCR4 displayed on paramagnetic proteoliposomes (PMPLs) to reduce non-specific gp120 binding – basic residues in the V3 loop and the beta19 strand (RIKQ, positions 419-422) were involved, and deletion of the V1-V2 loops allowed CD4-independent CXCR4 binding – MAbs 17b (CD4i) and F105 (CD4BS) were used to study conformational changes in the mutants – C11 was used to detect gp120 binding to CXCR4 or CCR5 on PMPLs. Basmaciogullari *et al.* [2002] (**antibody binding site definition and exposure**)
  - C11: HIV-1 gp160deltaCT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines – 2F5 bound to gp160deltaCT with a reconstituted membrane ten-fold better than the same protein on beads – anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160deltaCT PLs indistinguishably from gp160deltaCT expressed on the cell surface – non-neutralizing MAbs C11 and A32 bound with lower affinity than NAb IgG1b12 – the MAb 17b was sCD4 inducible on gp160deltaCT PL. Grundner *et al.* [2002] (**antibody binding site definition and exposure, vaccine antigen design**)
  - C11: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-299) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120

- Abs. Authors describe the epitope as N-term and C-term binding. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- C11: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibrin – stabilized oligomer gp140 delta683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**antibody binding site definition and exposure**)
  - C11: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**vaccine antigen design**)
  - C11: Does not compete with binding of MAb generated in response to gp120-CD4 complex, CG10. Sullivan *et al.* [1998b] (**antibody interactions**)
  - C11: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – C11 bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
  - C11: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
  - C11: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – partial re-exposure if sCD4 was bound – does not bind to HXBc2 gp120 if the 19 C-term amino acids are deleted. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
  - C11: Binding enhanced by anti-V3 MAb 5G11 – reciprocal inhibition with anti-C1 MAbs. Moore & Sodroski [1996] (**antibody interactions**)
  - C11: Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**antibody binding site definition and exposure**)
  - C11: Did not block ability of gp120-sCD4 complexes to inhibit MIP-1alpha binding – binds to gp41-binding domain. Wu *et al.* [1996] (**antibody binding site definition and exposure**)
  - C11: Mutations that inhibit binding: C1 (45 W/S, 88 N/P) – V5 (463 N/D) – and C5 (491 I/F, 493 P/K and 495 G/K) and enhance binding: C1 (36 V/L) – V1-V2 (152/153 GE/SM) – and DeltaV1/V2/V3. Moore *et al.* [1994d] (**antibody binding site definition and exposure**)
- No.** 1123  
**MAb ID** L81  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1)  
**Ab Type** gp120 C1-C5  
**References** Parren *et al.* 1997b; Ditzel *et al.* 1997
- L81: gp120 immobilized on solid phase by capture with anti-CD4 BS MAb L72 was used for selection of Fabs – L81 binding is abolished by C1 substitution 45 W/S, C5 substitution 491 I/F, and C3 substitution L/A. Ditzel *et al.* [1997]
  - L81: Does not neutralize TCLA strains or primary isolates. Parren *et al.* [1997b]
- No.** 1124  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location**  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 C3  
**References** Wang *et al.* 2002b
- Autologous NAbs were studied in 3 patients on HAART that rebounded – phylogenetic analysis of env (V1-V5) sequences indicated that rebound viruses had evolved from or preexisted in baseline populations – HIV-1 rebound viruses from all 3 patients were resistant to neutralization by autologous IgG, unlike the baseline viruses – mutations in the C3 region was responsible for conferring neutralization resistance against autologous antibody in 2 of 3 patients. Wang *et al.* [2002b]
- No.** 1125  
**MAb ID** 1024  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**  
**Ab Type** gp120 C4  
**References** Berman *et al.* 1997
- 1024: Binds to 1/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997]
- No.** 1126  
**MAb ID** 4KG5 (4KG.5)  
**HXB2 Location** Env



**Author Location** gp120 (JR-FL)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 V1-V2-V3

**References** Cham *et al.* 2006; Bowley *et al.* 2007; Selvarajah *et al.* 2005; Zwick *et al.* 2003

**Keywords** antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay standardization/improvement, binding affinity, neutralization, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 4KG5: Called 4KG.5. A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. 4KG5 was identified using both methods, and binds to a unique epitope that depends on V1, V2 and V3. Bowley *et al.* [2007] (**antibody binding site definition and exposure, antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)
- 4KG5: This Ab was shown to infrequently neutralize cloned Envs (clades A, B, C, D, F1, CRF01\_AE, CRF02\_AG, CRF06\_cpx and CRF11\_cpx) derived from donors with and without broadly cross-reactive neutralizing antibodies. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 4KG5: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. V1/V2/V3 MAb 4KG2, C1-C4 MAb A32, C1-C5 MAb C11, and HIVIG all either did not bind or had significantly diminished binding to both antigen constructs. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- 4KG5: 4KG5, a single-chain Fv (scFv), reacts with a conformational epitope that is formed by the V1, V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. 4KG5 was derived from the serum of HIV-1 infected patient FDA2, who showed broad neutralizing activity, but is not itself neutralizing. Denaturation of gp120 abolished binding of 4KG5 and Fab b12. Additionally, binding of 4KG5 was abrogated when any of the V1, V2 or V3 loops were deleted. Of a panel of Abs tested, only NAb b12 enhanced 4KG5 binding to gp120 JR-FL. MAbs to the following regions diminished or abrogated binding: V2 loop MAbs (G3-4, G3-136), V3 loop MAbs (19b, 447-52D, hNM01, AH48,

loop2, F425 B4e8, 694-88D), V3-C4 (G3-299, G3-42, G3-519, G3-537), CD4BS (b6, b3, F91, F105, 15e, L33, 1008-D, 654-30D, 559-64D, 1027-30D, Ia3, Ia7, FG39, Fbb14). MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1, V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. 4KG5 recognized HIV-1 envelope proteins derived from JR-FL, JR-CSF, BaL, ADA and R2, but not MN, DH123, HxB2, YU2, SF2 and 89.6. Binding of 4KG5 to different strains of HIV-1 env is probably due to sequence differences in V3 and C4, rather than V1 or V2. Zwick *et al.* [2003] (**antibody binding site definition and exposure, antibody generation, antibody interactions, variant cross-recognition or cross-neutralization, structure**)

**No.** 1127

**Mab ID** 23A (2.3A)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** no

**Immunogen**

**Species (Isotype)**

**Ab Type** gp120 C5

**Research Contact** James Robinson, Tulane University, LA

**References** Schulke *et al.* 2002; Binley *et al.* 1999; Fouts *et al.* 1997; Trkola *et al.* 1996a; Wu *et al.* 1996; Thali *et al.* 1993; Thali *et al.* 1992a

- 23A: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140. Schulke *et al.* [2002]
- 23A: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999]
- 23A: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric env binding – 23A bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997]

- 23A: C5 binding MAb – does not inhibit gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- 23A: Called 2.3A – Did not block ability of gp120-sCD4 complexes to inhibit MIP-1alpha binding – binds to gp41-binding domain of gp120. Wu *et al.* [1996]

**No.** 1128  
**MAb ID** D7324  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*HIV component:* gp120  
**Species (Isotype)** sheep  
**Ab Type** gp120 C5  
**Research Contact** Aalto BioReagents Ltd, Dublin, Ireland or Cliniqua Inc., Fallbrook, CA, USA

**References** Martín-García *et al.* 2005; Koefoed *et al.* 2005; Jeffs *et al.* 2004; Zwick *et al.* 2003; Herrera *et al.* 2003; Poignard *et al.* 2003; Basmaciogullari *et al.* 2002; Xiang *et al.* 2002a; Gram *et al.* 2002; Sanders *et al.* 2002; Binley *et al.* 1998; Mondor *et al.* 1998; Ugolini *et al.* 1997; Ditzel *et al.* 1997; Trkola *et al.* 1996a; Wyatt *et al.* 1995; Moore *et al.* 1993b; Moore *et al.* 1993a; Sattentau & Moore 1991; Moore 1990

**Keywords** antibody binding site definition and exposure, antibody interactions, subtype comparisons, vaccine antigen design

- D7324: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. D7324 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a C5 epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- D7324: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using F105, IgG1b12, 17b and 48d, 2G12 and 447-52D. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. The kinetics of D7324 binding were tested as a control, and were unchanged. Martín-García *et al.* [2005] (**antibody binding site definition and exposure**)
- D7324: A set of oligomeric envelope proteins were made from six primary isolates for potential use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore

folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. D7324 bound to clade A, B, C, D and F HIV-1 primary isolates, but not to the group O protein. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**vaccine antigen design, subtype comparisons**)

- D7324: Used to capture gp120 onto solid phase for epitope mapping. Basmaciogullari *et al.* [2002]; Binley *et al.* [1998]; Ditzel *et al.* [1997]; Herrera *et al.* [2003]; Moore *et al.* [1993a,b]; Poignard *et al.* [2003]; Sanders *et al.* [2002]; Xiang *et al.* [2002a]
- D7324: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a C5-binding polyclonal Ab that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- D7324: Called NEA9205 – gp120 capture ELISAs with MAbs D7324 (anti-C-term) or 9205 (anti-V3) were compared in a study of orientation of glycosylation sites – CD4 binding could only inhibit deglycosylation when gp120 was bound to the plate by D7324, not by 9205, while Abs from HIV-1 infected people inhibited deglycosylation most effectively when gp120 was caught by 9205. Gram *et al.* [2002]
- D7324: Epitope in C5 – Does not neutralize JR-FL nor block gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- D7324: Binds to the last 15 amino acids in gp120 – used for antigen capture ELISA. Wyatt *et al.* [1995]
- D7324: Binding unaltered by gp120 binding to sCD4, in contrast to 110.5, 9284, 50-69 and 98-6. Sattentau & Moore [1991]

**No.** 1129  
**MAb ID** 10/46c  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp120  
**Species (Isotype)** rat  
**Ab Type** gp120 CD4BS  
**References** Peet *et al.* 1998; Jeffs *et al.* 1996; Cordell *et al.* 1991

- 10/46c: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – 10/46c was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

- 10/46c: Increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996]

**No.** 1130  
**MAb ID** 1008-D  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 CD4BS  
**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrcr6.med.nyu), NYU Med Center, NY, NY

**References** Zwick *et al.* 2003; Zolla-Pazner *et al.* 1995

**Keywords** antibody interactions

- scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

**No.** 1131  
**MAb ID** 1027-30-D (1027-30D)  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp120 CD4BS  
**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrcr6.med.nyu) (NYU Med. Center)

**References** Gorny & Zolla-Pazner 2004; Zwick *et al.* 2003; Hioe *et al.* 2000

**Keywords** antibody interactions, review

- 1027-30D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1027-30-D: Called 1027-30D. scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of

the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

- 1027-30-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – anti-CD4 binding site MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – CD4BS MAbs 654-D, 559/64-D, 588-D, 830-D, 1027-30-D, and 1202-30D strongly diminished proliferation. Hioe *et al.* [2000]

**No.** 1132  
**MAb ID** 1125H (1125h)  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L (MN)  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp120 CD4BS  
**Research Contact** Shermaine Tilley, Public Health Research Institute, USA

**References** Yang *et al.* 1998; Alsmadi & Tilley 1998; Wyatt *et al.* 1998; Pincus *et al.* 1996; Warrior *et al.* 1996; D'Souza *et al.* 1995; Pinter *et al.* 1993b; Wyatt *et al.* 1992; Thali *et al.* 1992a; Tilley *et al.* 1991a; Tilley *et al.* 1991b

- 1125H: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against all four strains. Alsmadi & Tilley [1998]
- 1125H: Called 1125h – summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998]
- 1125H: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998]
- 1125H: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996]
- 1125H: Synergistic neutralization of HIV-1 when combined with anti-V2 MAb C108G. Warrior *et al.* [1996]
- 1125H: Neutralization was MN specific – failed to neutralize JRCSF, and 2 B subtype and 1 D subtype primary isolates in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995]
- 1125H: Binding to soluble gp120 enhanced by the presence of an anti-V3 HuMAb, 41148D. Pinter *et al.* [1993b]
- 1125H: Amino acid substitutions in HXB2 that strongly inhibit binding: 88, 102, 117, 113, 257, 368, 370, 421, 427, 457, 470, 480. Thali *et al.* [1992a]
- 1125H: Precipitation of Delta 297-329 env glycoprotein, with has a deleted V3 loop, is much more efficient than precipitation of wild type. Wyatt *et al.* [1992]

- 1125H: Binding to gp120 inhibited by CD4 – epitope is destroyed by reduction, but not by removal of N-linked sugars – potent neutralization of MN, RF, SF-2 and IIIB – neutralization synergy with anti-V3 MAb 4117C. Tilley *et al.* [1991a]

No. 1133

MAb ID 1125H (1125h)

HXB2 Location Env

Author Location gp120

Epitope

Subtype B

Neutralizing L (MN)

Immunogen HIV-1 infection

Species (Isotype) human (IgG1κ)

Ab Type gp120 CD4BS

Research Contact Shermaine Tilley, Public Health Research Institute, USA

References Pinter *et al.* 2004; Gorny & Zolla-Pazner 2004; Yang *et al.* 1998; Alsmadi & Tilley 1998; Wyatt *et al.* 1998; Pincus *et al.* 1996; Warriar *et al.* 1996; D'Souza *et al.* 1995; Pinter *et al.* 1993b; Wyatt *et al.* 1992; Thali *et al.* 1992a; Tilley *et al.* 1991a; Tilley *et al.* 1991b

Keywords ADCC, antibody binding site definition and exposure, antibody interactions, assay development, immunotoxin, review, structure, subtype comparisons, variant cross-recognition or cross-neutralization

- 1125H: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1125H: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-CD4BS MAbs were tested, including IgG1b12 which neutralizes both JRFL and SF162. The affinities for IgG1b12 and 5145A were similar for both JRFL and SF162, but 1125A bound with 2.5 fold higher affinity to SF162. 5145A and 1125H both preferentially neutralize SF162, but not JRFL, and the CD4BS is more sensitive to neutralization in the context of the SF162 V1V2 loop. This was also true for neutralization by sCD4. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 1125H: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIIB, MN, SF-2, and RF – bound and directed lysis against all four strains. Alsmadi & Tilley [1998] (**ADCC**)
- 1125H: Called 1125h – summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**structure**)

- 1125H: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998] (**assay development**)

- 1125H: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996] (**immunotoxin**)

- 1125H: Synergistic neutralization of HIV-1 when combined with anti-V2 MAb C108G. Warriar *et al.* [1996] (**antibody interactions**)

- 1125H: Neutralization was MN specific – failed to neutralize JRCSF, and 2 B subtype and 1 D subtype primary isolates in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

- 1125H: Binding to soluble gp120 enhanced by the presence of an anti-V3 HuMAb, 41148D. Pinter *et al.* [1993b] (**antibody interactions**)

- 1125H: Amino acid substitutions in HXB2 that strongly inhibit binding: 88, 102, 117, 113, 257, 368, 370, 421, 427, 457, 470, 480. Thali *et al.* [1992a] (**antibody binding site definition and exposure**)

- 1125H: Precipitation of Delta 297-329 env glycoprotein, with has a deleted V3 loop, is much more efficient than precipitation of wild type. Wyatt *et al.* [1992] (**antibody binding site definition and exposure**)

- 1125H: Binding to gp120 inhibited by CD4 – epitope is destroyed by reduction, but not by removal of N-linked sugars – neutralization of MN, RF, SF-2 and IIIB – neutralization synergy with anti-V3 MAb 4117C. Tilley *et al.* [1991a] (**antibody binding site definition and exposure, antibody interactions, variant cross-recognition or cross-neutralization**)

No. 1134

MAb ID 120-1B1

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing L

Immunogen

Species (Isotype) human

Ab Type gp120 CD4BS

Research Contact Virus Testing Systems Corp., Houston, TX

References Gorny & Zolla-Pazner 2004; Watkins *et al.* 1993

Keywords antibody binding site definition and exposure, review

- 120-1B1: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)

- 120-1B1: A neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – 120-1B1 was not affected by this mutation. Watkins *et al.* [1993] (**antibody binding site definition and exposure**)

**No.** 1135  
**MAb ID** 1202-D (1202-30-D)  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human (IgG1 $\kappa$ )  
**Ab Type** gp120 CD4BS  
**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrcr6.med.nyu) (NYU Med. Center)  
**References** Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Hioe *et al.* 2000; Nyambi *et al.* 1998  
**Keywords** review, subtype comparisons

- 1202-D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1202-D: Called 1202-30D – Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – anti-CD4 binding site MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – CD4BS MAbs 654-D, 559/64-D, 588-D, 830-D, 1027-30-D, and 1202-30D strongly diminished proliferation. Hioe *et al.* [2000]
- 1202-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1202-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – CD4-BS Abs tended to bind weakly without clade specificity to virions, but bound well to soluble gp120 – 1202-D did not bind to any B clade viruses, and weakly bound A, C, and G clade isolates – 559/64-D, 588-D and 1202-D had similar reactivities. Nyambi *et al.* [1998] (**subtype comparisons**)

**No.** 1136  
**MAb ID** 1331E  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\kappa$ )  
**Ab Type** gp120 CD4BS  
**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrcr6.med.nyu) (NYU Med. Center)  
**References** Gorny & Zolla-Pazner 2004; Gorny *et al.* 2000  
**Keywords** antibody binding site definition and exposure, review

- 1331E: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1331E: Inhibits sCD4 binding to rec gp120 LAI – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – CD4BS MAbs 559/64-D, 654-D, 729-D, 9CL and 1331E bound with a 5-13 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)

**No.** 1137  
**MAb ID** 1570 (1570A, 1570C, 1570D)  
**HXB2 Location** Env  
**Author Location** Env (PR12, BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 CD4BS  
**References** Gorny & Zolla-Pazner 2004; Jeffs *et al.* 2001  
**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1570: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1570: BH10 was mutated to form the PR12 protein with the first 74 C-terminal amino acids and the V1, V2 and V3 hypervariable loops deleted and a very well exposed CD4 binding domain (CD4bd) – this proteins was used to select three new human CD4BS MAbs 1570, 1595 and 1599 – three MAbs were isolated from one individual, 1570A, C and D but all were determined to have the same V(H)3 region – 1570 was able to bind to a panel of recombinant proteins from the A, B, C, D, and E subtypes. Jeffs *et al.* [2001] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 1138  
**MAb ID** 1595  
**HXB2 Location** Env  
**Author Location** Env (PR12, BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 CD4BS  
**References** Gorny & Zolla-Pazner 2004; Jeffs *et al.* 2001  
**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1595: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1595: BH10 was mutated to form the PR12 protein with the first 74 C-terminal amino acids and the V1, V2 and V3 hypervariable loops deleted and a very well exposed CD4 binding domain (CD4bd) – this proteins was used to select three new human CD4BS MAbs 1570, 1595 and 1599 – 1595 was able to bind gp120 from the A, B, and D clades from a panel of recombinant proteins from the A, B, C, D, and E subtypes. Jeffs *et al.* [2001] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1139  
**Mab ID** 1599  
**HXB2 Location** Env  
**Author Location** Env (PR12, BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 CD4BS  
**References** Gorny & Zolla-Pazner 2004; Jeffs *et al.* 2001  
**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1599: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 1599: BH10 was mutated to form the PR12 protein with the first 74 C-terminal amino acids and the V1, V2 and V3 hypervariable loops deleted and a very well exposed CD4 binding domain (CD4bd) – this proteins was used to select three new human CD4BS MAbs 1570, 1595 and 1599 – 1599 was able to bind gp120 only from the B clade from a panel of recombinant proteins from the A, B, C, D, and E subtypes. Jeffs *et al.* [2001] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1140  
**Mab ID** 15e (1.5e, 1.5E, 15E)  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp120 CD4BS  
**Research Contact** James Robinson, Tulane University, LA, and David Ho, ADARC, NY, NY  
**References** Nabatov *et al.* 2004; Pantophlet *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Raja *et al.* 2003; Pantophlet *et al.* 2003a; Kwong *et al.* 2002; Zhang *et al.* 2002; Xiang *et al.* 2002b;

Kolchinsky *et al.* 2001; Park *et al.* 2000; Sullivan *et al.* 1998a; Fouts *et al.* 1998; Trkola *et al.* 1998; Binley *et al.* 1998; Sullivan *et al.* 1998b; Parren *et al.* 1998a; Wyatt *et al.* 1998; Parren *et al.* 1997b; Berman *et al.* 1997; Wyatt *et al.* 1997; Li *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Wisniewski *et al.* 1996; McDougal *et al.* 1996; Trkola *et al.* 1996a; Poignard *et al.* 1996a; Moore & Sodroski 1996; McKeating *et al.* 1996; Lee *et al.* 1995; Sattentau & Moore 1995; Moore *et al.* 1994a; Moore *et al.* 1994b; Cook *et al.* 1994; Thali *et al.* 1994; Bagley *et al.* 1994; Wyatt *et al.* 1993; Watkins *et al.* 1993; Thali *et al.* 1993; Moore & Ho 1993; Takeda *et al.* 1992; Thali *et al.* 1992a; Wyatt *et al.* 1992; Ho *et al.* 1992; Koup *et al.* 1991; Ho *et al.* 1991b; Cordell *et al.* 1991; Thali *et al.* 1991; Robinson *et al.* 1990a

**Keywords** ADCC, adjuvant comparison, antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, brain/CSF, co-receptor, enhancing activity, review, structure, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 15e: UK Medical Research Council AIDS reagent: ARP3016.
- 15e: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 15e: A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4, R5, and X4 viruses were generated, and sCD4, 2G12 and b12 neutralization resistance patterns were modified by addition of the late stage V1V2, glycosylation changes, and charge in concert, while neutralization by 2F5 was unaffected. 15e, 17b, and 48d could not neutralize any of the variants tested. Nabatov *et al.* [2004] (**antibody binding site definition and exposure, co-receptor**)
- 15e: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 15e. Pantophlet *et al.* [2004] (**vaccine antigen design**)

- 15e: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
- 15e: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- 15e: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. CD4BS MAbs F105, 15e, and IgG1b12 as well as their Fab fragments inhibited CD4-independent binding of the V1/V2 loop-deleted gp120 glycoproteins of R5 HIV-1 isolates ADA, YU2 and JRFL and to CCR5 in a concentration dependent manner. Raja *et al.* [2003] (**co-receptor**)
- 15e: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 15e: Called 1.5e. Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- 15e: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**)
- 15e: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**)
- 15e: Mutations in two glycosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYRLINC-NTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, including to 15e. Kolchinsky *et al.* [2001] (**antibody binding site definition and exposure**)
- 15e: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000] (**antibody binding site definition and exposure**)
- 15e: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – CD4BS MAbs 15e, F91 and IgG1b12 bound better to the deleted protein than to wild type. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
- 15e: CD4BS MAbs 15e, 21h, and F91 bind with even lower affinity than 205-43-1 and 205-42-15 to JRFL oligomer. Fouts *et al.* [1998] (**antibody binding site definition and exposure**)
- 15e: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**antibody binding site definition and exposure**)

- 15e: Competes with CG-10 binding, a MAb raised against a gp120 CD4 complex, this was probably due to the disruption of CD4-gp120 by 15e. Sullivan *et al.* [1998b] (**antibody binding site definition and exposure, antibody interactions**)
- 15e: Called 1.5e – the HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – 1.5e enhances and does not neutralize YU2 env even at 50 ug/ml. Sullivan *et al.* [1998a] (**antibody binding site definition and exposure**)
- 15e: No detectable neutralizing activity among primary isolates with different co-receptor usage – some neutralization of TCLA strains. Trkola *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 15e: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**structure**)
- 15e: Called 1.5E – Binds to 7/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 15e: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 15e bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- 15e: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – 15e could only achieve 50% neutralization, but could act synergistically with anti-V3 MAb 694/98-D to achieve 90%. Li *et al.* [1997] (**antibody interactions**)
- 15e: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b]
- 15e: Does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-93, are deleted. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- 15e: Neutralizes HIV-1 LAI less potently than V3 specific MAbs. McDougal *et al.* [1996]
- 15e: Called 1.5e – Neutralizes HXB2, but fails to neutralize chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
- 15e: gp120 binding enhanced by anti-V3 MAb 5G11 and anti-V2 MAb G3-136 – binding inhibited by other CD4 binding site MAbs, antibodies that bind to gp120 only when CD4 is bound, and CD4-IgG. Moore & Sodroski [1996] (**antibody interactions**)
- 15e: Anti-CD4BS MAbs 15e, 21h, and IgG1b12 did not cause gp120 dissociation from virus, or exposure of the gp41 epitope of MAb 50-69, in contrast to CD4i MAb 48d and anti-V3 neutralizing MAbs. Poignard *et al.* [1996a] (**antibody interactions**)
- 15e: Inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**antibody binding site definition and exposure**)
- 15e: 15e is V H4 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996] (**antibody sequence variable domain**)
- 15e: The V4 and V5 domains are essential for 1.5e binding, in contrast to the V1, V2, and V3 loops. Lee *et al.* [1995] (**antibody binding site definition and exposure**)
- 15e: Binds with higher affinity to monomer than to oligomer, moderate association rate. Sattentau & Moore [1995] (**antibody binding site definition and exposure**)
- 15e: Heavy chain is V HIV, V2-1 – light chain is V<sub>kappa</sub>I, Hum01/012. Compared to 21h and F105. Bagley *et al.* [1994] (**antibody sequence variable domain**)
- 15e: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – anti-CD4 MAbs moderately inhibit gp120 binding to GalCer, possibly through steric hindrance – binding of GalCer to gp120 inhibited but did not completely block 15e binding. Cook *et al.* [1994] (**antibody binding site definition and exposure, brain/CSF**)
- 15e: Cross-reactive with gp120 proteins from clades B and D, less so with A and C, and not reactive with clade E and F. Moore *et al.* [1994b] (**subtype comparisons**)
- 15e: A mutation in gp41, 582 A/T, confers resistance to neutralization (also confers resistance to MAbs F105, 48d, 21h and 17b).. Thali *et al.* [1994] (**antibody binding site definition and exposure**)
- 15e: Conformational, does not bind denatured gp120 – neutralizes IIIB – reactive with SF-2 gp120 – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 15e: Called 15E – a neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – 15E neutralization was not affected by this mutation. Watkins *et al.* [1993] (**antibody binding site definition and exposure**)
- 15e: Binding to Delta V1/2 and Delta V1/2/3 mutant glycoproteins is greater than binding to wildtype gp120. Wyatt *et al.* [1993] (**antibody binding site definition and exposure**)
- 15e: gp120 mutants that affect 15e epitope binding: 113, 257, 368, 370, 421, 427, 475 – four of these coincide with amino acids important for the CD4 binding domain. Ho *et al.* [1992] (**antibody binding site definition and exposure**)
- 15e: Amino acid substitutions in HXB2 that strongly inhibit binding, similar to Ho *et al.* [1992], some additional, 88, 102, 117, 113, 257, 368, 370, 421, 427, 457, 470, 480 Thali *et al.* [1992a]. Ho *et al.* [1992]; Thali *et al.* [1992a] (**antibody binding site definition and exposure**)
- 15e: Called N70-1.5e – does not enhance infection of HIV-1 IIIB and MN. Thali *et al.* [1992a] (**enhancing activity**)
- 15e: Precipitation of Delta 297-329 env glycoprotein, with a deleted V3 loop, is much more efficient than precipitation of wild type. Wyatt *et al.* [1992] (**antibody binding site definition and exposure**)



- 15e: Cross-competes with MAbs ICR 39.13g and ICR 39.3b. Cordell *et al.* [1991] (**antibody interactions**)
- 15e: Broadly neutralizing, binds multiple strains, competes with CD4 for gp120 binding, DTT reduction of env abrogates binding – more potent blocking of gp120-sCD4 binding than MAbs G3-536 and G3-537. Ho *et al.* [1991b] (**adjuvant comparison, variant cross-recognition or cross-neutralization**)
- 15e: Binds to gp120 of HIV-1 IIIB, but not RF – mediates ADCC – deletion of the V3 loop from gp120 does not alter ADCC activity. Koup *et al.* [1991] (**ADCC, variant cross-recognition or cross-neutralization**)

No. 1141

**MAb ID** 21h (2.1H)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

Neutralizing L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1)

**Ab Type** gp120 CD4BS

**Research Contact** James Robinson, Tulane University, LA

**References** Gorny & Zolla-Pazner 2004; Xiang *et al.* 2002b; Fouts *et al.* 1998; Parren *et al.* 1998a; Wyatt *et al.* 1998; Parren *et al.* 1997b; Wyatt *et al.* 1997; Ugolini *et al.* 1997; Li *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; McKeating *et al.* 1996; Wisniewski *et al.* 1996; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Thali *et al.* 1994; Bagley *et al.* 1994; Moore *et al.* 1994a; Moore *et al.* 1994b; Moore & Ho 1993; Wyatt *et al.* 1993; Ho *et al.* 1992; Thali *et al.* 1992a; Ho *et al.* 1991b

**Keywords** acute/early infection, antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, binding affinity, review, structure, subtype comparisons, variant cross-recognition or cross-neutralization

- 21h: UK Medical Research Council AIDS reagent: ARP3017.
- 21h: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 21h: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations—375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced—IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced—2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope—another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**)
- 21h: CD4BS MAbs 15e, 21h, and F91 bind with even lower affinity than 205-43-1 and 205-42-15 to JRFL oligomer – conclusions of this paper contrast with Parren *et al.* [1998a] Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**binding affinity**)
- 21h: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- 21h: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**antibody binding site definition and exposure, structure**)
- 21h: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 21h bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- 21h: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – 50% neutralization could not be achieved at a maximal concentration of 67 mug/ml. Li *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 21h: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 21h: Viral binding inhibition by 21h strongly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5). Ugolini *et al.* [1997] (**antibody binding site definition and exposure**)
- 21h: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding – major deletions in C1 and C5 and deletions of the V1V2 and V3 loops do not diminish binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- 21h: Called 2.1H – Neutralizes HXB2, but fails to neutralize chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996] (**variant cross-recognition or cross-neutralization**)
- 21h: Anti-CD4 binding site MAb – reciprocal inhibition by anti-C1, -C4 and other anti-CD4 binding site antibodies – enhanced by some anti-V2 MAbs and anti-V3 MAb 5G11 – enhances binding of some anti-V3 and -V2 MAbs. Moore & Sodroski [1996] (**antibody interactions**)
- 21h: Anti-CD4BS MAbs 15e, 21h, and IgG1b12 did not cause gp120 dissociation from virus, or exposure of the gp41 epitope of MAb 50-69, in contrast to CD4i MAb 48d and anti-V3 neutralizing MAbs. Poignard *et al.* [1996a] (**antibody binding site definition and exposure, antibody interactions**)
- 21h: 21h is V H3 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996] (**antibody sequence variable domain**)

- 21h: Binds with higher affinity to monomer than to oligomer, moderate association rate. Sattentau & Moore [1995] (**antibody binding site definition and exposure**)
- 21h: Heavy chain is V HIII, VDP-35 – light chain is V<sub>lambda</sub>IIIa, Hum318. Compared to 15e and F105. Bagley *et al.* [1994] (**antibody sequence variable domain**)
- 21h: Has strong cross-reactivity with gp120 monomers from most subtypes, A-F, with the least reactivity to clade E. Moore *et al.* [1994b] (**subtype comparisons**)
- 21h: Competition studies with human sera from seroconverting individuals showed that anti-CD4 BS antibodies can arise very early in infection, comparable or prior to anti-V3 antibodies. Moore *et al.* [1994a] (**acute/early infection**)
- 21h: A mutation in gp41, 582 A/T, confers resistance to neutralization (also confers resistance to MAbs F105, 48d, 15e and 17b). Thali *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 21h: Conformational, does not bind denatured gp120 – neutralizes IIIB – reactive with SF-2 gp120 – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993] (**antibody binding site definition and exposure**)
- 21h: Binding to Delta V1/2 and Delta V1/2/3 mutant glycoproteins is greater than binding to wildtype gp120. Wyatt *et al.* [1993] (**antibody binding site definition and exposure**)
- 21h: Amino acid substitutions in HXB2 that inhibit binding, some shared with CD4 binding inhibition, 88, 113, 257, 368, 370, 421, 470, 480. Thali *et al.* [1992a] (**antibody binding site definition and exposure**)

No. 1142

Mab ID 28A11/B1

HXB2 Location Env

Author Location gp120 (SF162)

Epitope

Subtype B

Neutralizing L

Immunogen vaccine

*Vector/Type:* protein *Strain:* B clade SF162*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

Species (Isotype) transgenic mouse (IgG2κ)

Ab Type gp120 CD4BS

Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

References Gorny & Zolla-Pazner 2004; He *et al.* 2002

Keywords review, subtype comparisons, variant cross-recognition or cross-neutralization

- 28A11/B1: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 28A11/B1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—28A11/B1 was one of these

four MAbs. He *et al.* [2002] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1143

Mab ID 2G6

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing

Immunogen

Species (Isotype)

Ab Type gp120 CD4BS

Research Contact Herman Katinger, Inst. Appl. Microbiol. University of Agricultural Science, or Polymun Scientific Inc., Vienna, Austria

References Gorny & Zolla-Pazner 2004; Parren *et al.* 1998a; Fouts *et al.* 1998

Keywords antibody binding site definition and exposure, review, variant cross-recognition or cross-neutralization

- 2G6: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 2G6: Binds to JRFL oligomer with an affinity comparable to IgG1b12, but does not neutralize the virus, so binding of oligomer is not always predictive of neutralization – conclusions of this paper contrast with Parren *et al.* [1998a] – authors propose a model where 205-46-9 and 2G6 may inhibit CD4 binding, but cause a conformational shift which enhances CCR5 binding and thus counteracts the neutralizing effect Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)

No. 1144

Mab ID 35F3/E2

HXB2 Location Env

Author Location gp120 (SF162)

Epitope

Subtype B

Neutralizing L

Immunogen vaccine

*Vector/Type:* protein *Strain:* B clade SF162*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

Species (Isotype) transgenic mouse (IgG2κ)

Ab Type gp120 CD4BS

Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

References Gorny & Zolla-Pazner 2004; He *et al.* 2002

Keywords review, subtype comparisons, variant cross-recognition or cross-neutralization

- 35F3/E2: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)

- 35F3/E2: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2 $\kappa$  MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—35F3/E2 was one of these four MAbs. He *et al.* [2002] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1145

MAb ID 38G3/A9

HXB2 Location Env

Author Location gp120 (SF162)

Epitope

Subtype B

Neutralizing L

Immunogen vaccine

*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

Species (Isotype) transgenic mouse (IgG2 $\kappa$ )

Ab Type gp120 CD4BS

Research Contact Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

References Gorny & Zolla-Pazner 2004; He *et al.* 2002

Keywords variant cross-recognition or cross-neutralization

- 38G3/A9: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**)
- 38G3/A9: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2 $\kappa$  MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—38G3/A9 was one of these four MAbs. He *et al.* [2002] (**variant cross-recognition or cross-neutralization**)

No. 1146

MAb ID 428

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing

Immunogen HIV-1 infection

Species (Isotype) human

Ab Type gp120 CD4BS

References Jeffs *et al.* 1996; Karwowska *et al.* 1992a

- 428: Slight, not significant increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996]

No. 1147

MAb ID 448-D (448D)

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing L

Immunogen HIV-1 infection

Species (Isotype) human (IgG1 $\lambda$ )

Ab Type gp120 CD4BS

Research Contact Susan Zolla-Pazner (Zollas01@mrcr6.med.nyu), NYU Med Center, NY, NY

References Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Wyatt *et al.* 1998; Li *et al.* 1997; Manca *et al.* 1995a; Forthal *et al.* 1995; Laal *et al.* 1994; Spear *et al.* 1993; McKeating *et al.* 1992c; Karwowska *et al.* 1992a

Keywords ADCC, antibody binding site definition and exposure, antibody interactions, complement, enhancing activity, review, structure, subtype comparisons, variant cross-recognition or cross-neutralization

- 448-D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 448-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- 448-D: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**structure**)
- 448-D: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env. Li *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 448-D: Neutralizing activity, positive ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC, enhancing activity**)
- 448-D: Virions complexed to gp120 Ab facilitate presentation of p66 RT epitopes to Th cells. Manca *et al.* [1995a]
- 448-D: Dissociation constant gp120 IIIB 0.029 – neutralizes IIIB, acts synergistically with anti-V3 MAb 447-52D. Laal *et al.* [1994] (**antibody interactions**)
- 448-D: Did not mediate deposition of complement component C3 on HIV infected cells. Spear *et al.* [1993] (**complement**)
- 448-D: Conformational – reactive with IIIB gp120 in RIP, but not WB assay. Karwowska *et al.* [1992a] (**antibody binding site definition and exposure**)
- 448-D: Called 448D – blocks gp120-CD4 binding – substitutions at gp120 residues 88, 113, 117, 257, 368 and 370 reduce binding – epitope similar to rat MAbs 39.13g and 39.3b. McKeating *et al.* [1992c] (**antibody binding site definition and exposure**)

**No.** 1148  
**MAb ID** 46D2/D5  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** transgenic mouse (IgG2κ)  
**Ab Type** gp120 CD4BS  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

- References** He *et al.* 2002
- 44D2/D5: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—44D2/D5 could not neutralize autologous SF162, and while it was cross-reactive, it was at lower affinity. He *et al.* [2002]

**No.** 1149  
**MAb ID** 48-16  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgGκ)  
**Ab Type** gp120 CD4BS  
**References** Gorny & Zolla-Pazner 2004; Fevrier *et al.* 1995

- Keywords** antibody binding site definition and exposure, binding affinity, review, variant cross-recognition or cross-neutralization
- 48-16: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database. Most neutralize TCLA strains only, 48-16 is one of four that are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
  - 48-16: Broadly cross-reactive, reacts outside the CD4 binding site and V3 region—competes with sera from 45 seropositive subjects—binding affinity  $2-5 \times 10^{-9}$  M. Fevrier *et al.* [1995] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, binding affinity**)

**No.** 1150  
**MAb ID** 50-61A  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgGκ)

**Ab Type** gp120 CD4BS  
**References** Gorny & Zolla-Pazner 2004; Fevrier *et al.* 1995

- Keywords** binding affinity, review, variant cross-recognition or cross-neutralization
- 50-61A: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
  - 50-61A: Neutralizes lab strains LAI and SF2 – competes with sera from 45 seropositive subjects – binding affinity  $2.4 \times 10^{-10}$  M. Fevrier *et al.* [1995] (**variant cross-recognition or cross-neutralization, binding affinity**)

**No.** 1151  
**MAb ID** 5145A  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Subtype** B  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1)  
**Ab Type** gp120 CD4BS  
**Research Contact** Abraham Pinter, Public Health Research Institute, Newark, NJ, 07103. pinter@phri.org  
**References** Pinter *et al.* 2005; Pinter *et al.* 2004; Gorny & Zolla-Pazner 2004; He *et al.* 2002; Alsmadi & Tilley 1998; Pincus *et al.* 1996; Warrier *et al.* 1996; Pinter *et al.* 1993a

- Keywords** ADCC, anti-idiotypic, antibody binding site definition and exposure, antibody interactions, immunotoxin, variant cross-recognition or cross-neutralization
- 5145A: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potentially neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MAbs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. A modification in the NAb sensitive isolate SF162 to introduce the C108g epitope, including the introduction of a glycosylation site (160-161 KV -> NI) and 167-169 NKM -> GKV, decreased neutralization sensitivity to 5145A more than 50-fold. 5145A is a disulfide-dependent epitope in the CD4 binding domain that is lost after reduction; C108g, contrary to earlier reports, was also shown to require disulfide bonds. Pinter *et al.* [2005] (**anti-idiotypic, antibody binding site definition and exposure**)
  - 5145A: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization**)
  - 5145A: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL

is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-CD4BS MAbs were tested, including IgG1b12, which neutralizes both JRFL and SF162. The affinities for IgG1b12 and 5145A were similar for both JRFL and SF162, but 1125A bound with 2.5 fold higher affinity to SF162. 5145A and 1125H both preferentially neutralize SF162, but not JRFL, and the CD4BS is more sensitive to neutralization in the context of the SF162 V1V2 loop. This was also true for neutralization by sCD4. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)

- 5145A: Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A, 4117C and 697D were used as controls. He *et al.* [2002]
- 5145A: A study of 6 anti-Env MAbs and their ability to bind or direct ADCC against target cells infected with IIB, MN, SF-2, and RF – bound and directed lysis against all four strains. Alsmadi & Tilley [1998] (**ADCC**)
- 5145A: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996] (**immunotoxin**)
- 5145A: Synergistic neutralization of HIV-1 when combined with anti-V2 MAb C108G. Warrior *et al.* [1996] (**antibody interactions**)
- 5145A: Potent and broadly cross-reactive neutralization of lab strains. Pinter *et al.* [1993a] (**variant cross-recognition or cross-neutralization**)

No. 1152

**MAb ID** 558-D

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu), NYU Med Center, NY, NY

**References** Gorny & Zolla-Pazner 2004; Nyambi *et al.* 1998; McKeating *et al.* 1992c

**Keywords** antibody binding site definition and exposure, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 558-D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 558-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – CD4BS Abs tended to bind

weakly without clade specificity to virions, but bound well to soluble gp120 – 558-D did not bind to any B clade viruses, and weakly bound to clade A, C, and G isolates – 559/64-D, 558-D and 1202-D had similar reactivities. Nyambi *et al.* [1998] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

- 558-D: Blocks gp120-CD4 binding – binds a panel of mutants all except for 256 S/Y and 262 N/T, which are probably conformationally disruptive. McKeating *et al.* [1992c] (**antibody binding site definition and exposure**)

No. 1153

**MAb ID** 559/64-D (559, 559-64D)

**HXB2 Location** Env

**Author Location** gp120 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 CD4BS

**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu), NYU Med Center, NY, NY

**References** Gorny & Zolla-Pazner 2004; Zwick *et al.* 2003; York *et al.* 2001; Hioe *et al.* 2001; Nyambi *et al.* 2000; Hioe *et al.* 2000; Gorny *et al.* 2000; Nyambi *et al.* 1998; Hioe *et al.* 1997b; Hioe *et al.* 1997a; Jeffs *et al.* 1996; Forthal *et al.* 1995; Stamatatos & Cheng-Mayer 1995; Spear *et al.* 1993; McKeating *et al.* 1992c; Karwowska *et al.* 1992a

**Keywords** ADCC, antibody binding site definition and exposure, antibody interactions, assay development, complement, enhancing activity, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 559/64D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 559/64D: called 559-64D: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 559/64-D: CD4BS MAbs when complexed with gp120, inhibit proliferation of gp120-specific CD4 T-cells and IFNγ production—anti-CD4BS MAbs inhibit gp120 presentation by altering the uptake and/or processing of gp120 by the APCs, not by blocking of gp120 attachment to CD4 on the surface of APCs. Hioe *et al.* [2001]

- 559/64-D: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4 induced or CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 559/64-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – CD4BS MAbs 559/64-D, 654-D, 729-D, 9CL and 1331E bound with a 5-13 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 559/64-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – anti-CD4 binding site MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – CD4BS MAbs 654-D, 559/64-D, 588-D, 830-D, 1027-30-D, and 1202-30D strongly diminished proliferation. Hioe *et al.* [2000]
  - 559/64-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12. Nyambi *et al.* [2000] (**subtype comparisons**)
  - 559/64-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – CD4BS Abs tended to bind weakly without clade specificity to virions, but bound well to soluble gp120 – 559/64-D did not bind to any B clade viruses, and weakly bound clade A, C, and G isolates – 559/64-D, 558-D and 1202-D had similar reactivities. Nyambi *et al.* [1998] (**antibody binding site definition and exposure, subtype comparisons**)
  - 559/64-D: Used in the development of resting cell neutralization assay. Hioe *et al.* [1997a] (**assay development**)
  - 559/64-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
  - 559/64-D: Called 559 – slight, not significant increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996] (**antibody binding site definition and exposure**)
  - 559/64-D: Neutralizing activity, no ADCC activity, and no viral enhancing activity. Forthal *et al.* [1995] (**ADCC, enhancing activity, variant cross-recognition or cross-neutralization**)
  - 559/64-D: Called 559-64D – The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – CD4BS loop epitopes are somewhat occluded in the oligomeric gp120 epitopes on the virion surface relative to the gp120 monomer as indicated by an increase in the half-maximal binding values to macrophage-tropic isolates SF162 and SF128a and to T-cell tropic SF2 – binding of anti-CD4BS MAbs to SF2 resulted in a significant amount of dissociation of gp120 from virion surface. Stamatatos & Cheng-Mayer [1995] (**antibody binding site definition and exposure**)
  - 559/64-D: Did not mediate deposition of complement component C3 on HIV infected cells. Spear *et al.* [1993] (**complement**)
  - 559/64-D: Conformational – reactive with IIIB gp120 in RIP, but not WB assay. Karwowska *et al.* [1992a] (**antibody binding site definition and exposure**)
- No. 1154  
**MAb ID** 55D5/F9  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** transgenic mouse (IgG2κ)  
**Ab Type** gp120 CD4BS  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org  
**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002  
**Keywords** review, variant cross-recognition or cross-neutralization
- 55D5/F9: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database. Most neutralize TCLA strains only, this is one of four that are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
  - 55D5/F9: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—55D5/F9 was one of these four MAbs. He *et al.* [2002] (**variant cross-recognition or cross-neutralization**)

**No.** 1155  
**MAb ID** 588-D (588)  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp120 CD4BS

**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrcr6.med.nyu), NYU Med Center, NY, NY

**References** Nyambi *et al.* 2000; Hioe *et al.* 2000; Nyambi *et al.* 1998; Jeffs *et al.* 1996; Moore & Ho 1993; Buchbinder *et al.* 1992; Karwowska *et al.* 1992a

- 588-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – anti-CD4 binding site MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – CD4BS MAbs 654-D, 559/64-D, 588-D, 830-D, 1027-30-D, and 1202-30D strongly diminished proliferation. Hioe *et al.* [2000]
- 588-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12. Nyambi *et al.* [2000]
- 588-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – CD4-BS Abs tended to bind weakly without clade specificity to virions, but bound well to soluble gp120 – 588-D did not bind to any B clade viruses, and weakly bound a clade A, C, and G clade isolate – 559/64-D, 558-D and 1202-D reacted had similar reactivities. Nyambi *et al.* [1998]
- 588-D: Called 588 – slight, not significant increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996]
- 588-D: Weak neutralization of IIIB – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993]
- 588-D: 4-fold increase in neutralization potency for 588-D when combined 1:1 with human MAb 447-D. Buchbinder *et al.* [1992]
- 588-D: Conformational – reactive with IIIB gp120 in RIP, but not WB assay. Karwowska *et al.* [1992a]

**No.** 1156  
**MAb ID** 654-D (654-30D, 654/30D, 654-D100, 654.30D, 654)  
**HXB2 Location** Env  
**Author Location** gp120 (LAI)  
**Epitope**  
**Subtype** B  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgGκ)  
**Ab Type** gp120 CD4BS

**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrcr6.med.nyu), NYU Med Center, NY, NY

**References** Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Zwick *et al.* 2003; Gorny *et al.* 2002; Verrier *et al.* 2001; Nyambi *et al.* 2000; Hioe *et al.* 2001; Hioe *et al.* 2000; Gorny *et al.* 2000; Hioe *et al.* 1999; Stamatatos & Cheng-Mayer 1998; Nyambi *et al.* 1998; Schonning *et al.* 1998; Gorny *et al.* 1998; Hioe *et al.* 1997b; Gorny *et al.* 1997; Stamatatos *et al.* 1997; Li *et al.* 1997; Stamatatos & Cheng-Mayer 1995; Gorny *et al.* 1994; Laal *et al.* 1994; Karwowska *et al.* 1993

**Keywords** antibody binding site definition and exposure, antibody interactions, binding affinity, dendritic cells, enhancing activity, kinetics, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 654-D: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 654-D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 654-D: Called 654-30D. scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- 654-D: Called 654: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions and the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), and MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) Gorny *et al.* [2002]
- 654-D: CD4BS MAbs when complexed with gp120, inhibit proliferation of gp120-specific CD4 T-cells and IFN gamma production – anti-CD4BS MAbs inhibit gp120 presentation by altering the uptake and/or processing of gp120 by the APCs,

not by blocking of gp120 attachment to CD4 on the surface of APCs. Hioe *et al.* [2001]

- 654-D: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6—six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D, while six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281—no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions, variant cross-recognition or cross-neutralization**)
- 654-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – CD4BS MAbs 559/64-D, 654-D, 729-D, 9CL and 1331E bound with a 5-13 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 654-D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – CD4BS MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – MAb 654-D strongly diminished proliferation – there is a discrepancy in isotyping this antibody, previous reports indicated IgG1kappa, while Hioe suggests it is IgG1lambda. Hioe *et al.* [2000]
- 654-D: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12 – 654-D had the weakest binding among CD4BS MAbs, binding to only 4/26 isolates. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- 654-D: The presence of leukocyte function-associated molecule 1 (LFA-1) promotes virus infectivity and hinders neutralization, and anti-LFA-1 MAbs can enhance the neutralizing effect of anti-HIV V3 MAb 447-52D and anti-HIV CD4BS MAb IgG1b12 – non-neutralizing anti-HIV CD4BS MAb 654-D did not become neutralizing in the presence of anti-LFA-1 MAbs. Hioe *et al.* [1999]
- 654-D: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – CD4-BS Abs tended to bind very weakly without clade specificity to virions, but bound well to soluble gp120 – 654-D bound only to JRFL. Nyambi *et al.* [1998] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- 654-D: Called 654-D100 – 654-D100 and IgG1b12 neutralized viruses HIV-BRU and a mutated virus that lacks the V3 loop glycan equally effectively – in contrast, sera from guinea pigs immunized with BRU gp120 neutralize viruses more effectively that lack the V3 glycan. Schonning *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
- 654-D: Called 654.30D – deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its

neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V2 but not V1 slightly allowed neutralization by CD4BS MAb 654.30D. Stamatatos & Cheng-Mayer [1998] (**antibody binding site definition and exposure, subtype comparisons**)

- 654-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 654-D: Called 654-30D – One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env. Li *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 654-D: Anti-CD4 BS MAb 654-30D and IgG1b12 have comparable binding affinities, neither mediates gp120-virion dissociation, but IgG1b12 can neutralize SF128A and SF162 and 654-D cannot – 654-D actually enhances infection by both viruses in primary macrophages. Stamatatos *et al.* [1997] (**enhancing activity, binding affinity**)
- 654-D: Called 654-30D – The binding of conformation-dependent anti-V2, anti-V3, and anti-CD4BS MAbs to monomeric and virion-associated gp120 from HIV-1 isolates with differences in cell tropism was studied – CD4BS loop epitopes are somewhat occluded in the oligomeric gp120 epitopes on the virion surface relative to the gp120 monomer as indicated by an increase in the half-maximal binding values to macrophage-tropic isolates SF162 and SF128a and to T-cell tropic SF2 – binding of anti-CD4BS MAbs to SF2 resulted in a significant amount of dissociation of gp120 from virion surface. Stamatatos & Cheng-Mayer [1995] (**antibody binding site definition and exposure**)
- 654-D: Mild oxidation of carbohydrate moieties inhibits binding. Gorny *et al.* [1994] (**antibody binding site definition and exposure**)
- 654-D: Dissociation constant gp120 IIIB 0.008 – neutralizes IIIB, acts synergistically with anti-V3 MAb 447-52D – reported to be human(IgG1lambda) Laal *et al.* [1994] (**antibody interactions, kinetics**)

No. 1157

MAb ID 67G6/C4

HXB2 Location Env

Author Location gp120 (SF162)

Epitope

Subtype B

Neutralizing no

Immunogen vaccine



*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 CD4BS

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** review, variant cross-recognition or cross-neutralization

- 67G6/C4: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database. Most neutralize TCLA strains only, this MAb is one of four that are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 67G6/C4: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2κ MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120—6 anti-CD4BS MAbs competed with anti-CD4BS MAb 5145A, blocked sCD4 binding and were conformationally sensitive—4/6 could neutralize the autologous strain SF162, and were broadly cross-reactive with B clade R5 and X4 strains (not E clade)—67G6/C4 could not neutralize autologous SF162, and its binding was strain-specific. He *et al.* [2002] (**variant cross-recognition or cross-neutralization**)

**No.** 1158

**Mab ID** 729-D (729-30D)

**HXB2 Location** Env

**Author Location** gp120 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 CD4BS

**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrc6.med.nyu), NYU Med Center, NY, NY

**References** Gorny & Zolla-Pazner 2004; Gorny *et al.* 2000; Parren *et al.* 1997b; Li *et al.* 1997; D'Souza *et al.* 1997; Laal *et al.* 1994

**Keywords** antibody binding site definition and exposure, antibody interactions, kinetics, review, variant cross-recognition or cross-neutralization

- 729-D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 729-D: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – CD4BS MAbs 559/64-D, 654-D, 729-D, 9CL and 1331E bound with a 5-13 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)

- 729-D: In a multilaboratory blinded study, failed to consistently neutralize any of nine B clade primary isolates – reported here to have a lambda light chain, but originally reported in Laal *et al.* [1994] to be IgG1κ D'Souza *et al.* [1997]. D'Souza *et al.* [1997]; Laal *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 729-D: Called 720-30D – one of 14 human MAbs tested for ability to neutralize chimeric SHIV-vpu+, which expressed HIV-1 IIIB env. Li *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- 729-D: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 729-D: Dissociation constant gp120 IIIB 0.025 – neutralizes IIIB, acts synergistically with anti-V3 MAb 447-52D. Laal *et al.* [1994] (**antibody interactions, kinetics**)

**No.** 1159

**Mab ID** 830D (830-D)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen**

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Hioe *et al.* 2000; Wyatt *et al.* 1998; Hioe *et al.* 1997b

**Keywords** review, structure, variant cross-recognition or cross-neutralization

- 830D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 830D: Ab responses, because of their capacity to alter antigen uptake and processing, can influence helper T cell responses – anti-CD4 binding site MAbs or serum Ig from HIV+ individuals inhibited proliferative responses of gp120 specific T cells – CD4BS MAbs 654-D, 559/64-D, 588-D, 830-D, 1027-30-D, and 1202-30D strongly diminished proliferation. Hioe *et al.* [2000]
- 830D: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**structure**)
- 830D: Called 830-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera or plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D) and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by

a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

**No.** 1160  
**MAb ID** 9CL  
**HXB2 Location** Env  
**Author Location** gp120 (LAI)  
**Epitope Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 CD4BS  
**Research Contact** Susan Zolla-Pazner (Zollas01@mccr6.med.nyu), NYU Med Center, NY, NY

**References** Gorny & Zolla-Pazner 2004; Gorny *et al.* 2000

**Keywords** antibody binding site definition and exposure, review

- 9CL: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- 9CL: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – CD4BS MAbs 559/64-D, 654-D, 729-D, 9CL and 1331E bound with a 5-13 fold preference for the oligomer. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)

**No.** 1161  
**MAb ID** BM12  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 CD4BS  
**References** Kessler *et al.* 1995

- BM12: Broad cross-clade neutralization of primary isolates – additive effect in combination with MAb 2F5. Kessler *et al.* [1995]

**No.** 1162  
**MAb ID** D20  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type: vaccinia Strain: B clade IIIB HIV component: oligomeric gp140*  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1997; Otteken *et al.* 1996; Richardson *et al.* 1996; Broder *et al.* 1994; Earl *et al.* 1994

**Keywords** antibody binding site definition and exposure, antibody generation

- D20: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D20 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4. Sugiura *et al.* [1999] (**antibody binding site definition and exposure**)
- D20: Used for comparison in a study of gp41 antibodies – D20 binds to a greater extent to cell surface expressed Env than any of 38 conformation dependent anti-gp41 MAbs. Earl *et al.* [1997] (**antibody binding site definition and exposure**)
- D20: Pulse label experiments of 4 MAbs (D20, D27, T20, and T22) binding to noncleavable gp160 revealed that these anti-CD4 MAbs bound with a delay, and that the epitope formed with a t 1/2 of about 10 minutes. Otteken *et al.* [1996]
- D20: Human sera blocked binding in oligomeric ELISA assay to a similar extent for gp41 MAbs D20, D43, D61, and T4. Richardson *et al.* [1996]
- D20: Binding completely blocked by pooled human sera. Broder *et al.* [1994]
- D20: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

**No.** 1163  
**MAb ID** D21  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type: vaccinia Strain: B clade IIIB HIV component: oligomeric gp140*

**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D21: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D21 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4. Sugiura *et al.* [1999]
- D21: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1164  
**MAb ID** D24  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**

**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D24: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D24 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D24: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1165  
**MAB ID** D25  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**

**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D25: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D25 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4. Sugiura *et al.* [1999]
- D25: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1166  
**MAB ID** D28  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**

**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D28: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D28 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D28: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1167

**MAB ID** D35

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D35: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D35 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D35: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1168

**MAB ID** D39

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D39: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D39 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4. Sugiura *et al.* [1999]
- D39: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1169

**MAB ID** D42

**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D42: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D42 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D42: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1170

**MAb ID** D52

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D52: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D52 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D52: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1171

**MAb ID** D53

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D53: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D53 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D53: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1172

**MAb ID** D60

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Richardson *et al.* 1996; Earl *et al.* 1994

- D60: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D60 is part of a group of MAbs labeled B-I, that had limited cross-reactivity – of seven clade B isolates BH8 and B-al were they only two that consistently reacted with B-I MAbs – B-I MAbs fully blocked CD4 binding. Sugiura *et al.* [1999]
- D60: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1173

**MAb ID** DA48

**HXB2 Location** Env

**Author Location** gp120 (BRU)

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Sullivan *et al.* 1998a; Parren *et al.* 1998a

**Keywords** antibody binding site definition and exposure, antibody generation, binding affinity, review, variant cross-recognition or cross-neutralization

- DO8i: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- DA48: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization

were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)

- DA48: The HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – Fab Ab fragment DA48 also enhances YU2 entry, ruling out Fc interactions or Env cross-linking as a mechanism – while DA48 enhances YU2, it neutralizes HXBc2 – DA48 was obtained by panning libraries derived from bone marrow from a >15 year long term non-progressor against BRU gp120. Sullivan *et al.* [1998a] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization**)

No. 1174

**MAb ID** DO8i

**HXB2 Location** Env

**Author Location** gp120 (BRU)

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Sullivan *et al.* 1998a; Parren *et al.* 1998a

- DO8i: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- DO8i – the HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – Fab fragment DO8i also enhances YU2 entry, ruling out Fc interactions or Env cross-linking as a mechanism, while neutralizing HXBc2 – DO8i was obtained by panning libraries derived from bone marrow from a long term asymptomatic donor against BRU gp120. Sullivan *et al.* [1998a]

No. 1175

**MAb ID** F105 (F-105)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 CD4BS

**Research Contact** Marshall Posner, Boston MA

- References** Holl *et al.* 2006a; Wilkinson *et al.* 2005; Selvarajah *et al.* 2005; Martín-García *et al.* 2005; Pantophlet *et al.* 2004; Ling *et al.* 2004; Biorn *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Ohagen *et al.* 2003; Raja *et al.* 2003; Xiang *et al.* 2003; Poignard *et al.* 2003; Pantophlet *et al.* 2003a; Choe *et al.* 2003; Kwong *et al.* 2002; Ferrantelli *et al.* 2004a; Cavacini *et al.* 2002; Ling *et al.* 2002; Liu *et al.* 2002; Ferrantelli & Ruprecht 2002; Zhang *et al.* 2002; Basmaciogullari *et al.* 2002; Grundner *et al.* 2002; Edwards *et al.* 2002; Xiang *et al.* 2002b; Chakrabarti *et al.* 2002; Xu *et al.* 2002; Yang *et al.* 2002; York *et al.* 2001; Kolchinsky *et al.* 2001; Si *et al.* 2001; Yang *et al.* 2000; Park *et al.* 2000; Fortin *et al.* 2000; Baba *et al.* 2000; Robert-Guroff 2000; Oscherwitz *et al.* 1999a; Cavacini *et al.* 1999; Giraud *et al.* 1999; Sugiura *et al.* 1999; Kropelin *et al.* 1998; Sullivan *et al.* 1998a; Brand *et al.* 1998; Cavacini *et al.* 1998a; Li *et al.* 1998; Cavacini *et al.* 1998b; Wyatt *et al.* 1998; Wyatt *et al.* 1997; Cao *et al.* 1997b; Li *et al.* 1997; D'Souza *et al.* 1997; Parren *et al.* 1997b; Chen *et al.* 1996; Litwin *et al.* 1996; Pincus *et al.* 1996; Wisniewski *et al.* 1996; McDougal *et al.* 1996; Wolfe *et al.* 1996; Jagodzinski *et al.* 1996; Khouri *et al.* 1995; Sullivan *et al.* 1995; Cavacini *et al.* 1995; Posner *et al.* 1995; Turbica *et al.* 1995; Chen *et al.* 1994a; Earl *et al.* 1994; Cavacini *et al.* 1994a; Cavacini *et al.* 1994b; Cook *et al.* 1994; Thali *et al.* 1994; Bagley *et al.* 1994; Marasco *et al.* 1993; Watkins *et al.* 1993; Pincus *et al.* 1993; Klasse *et al.* 1993a; Potts *et al.* 1993; Montefiori *et al.* 1993; Wyatt *et al.* 1993; Cavacini *et al.* 1993b; Cavacini *et al.* 1993a; Posner *et al.* 1993; Moore & Ho 1993; Posner *et al.* 1992a; Posner *et al.* 1992b; Wyatt *et al.* 1992; Marasco *et al.* 1992; Thali *et al.* 1992a; Thali *et al.* 1991; Posner *et al.* 1991

**Keywords** ADCC, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, brain/CSF, co-receptor, complement, dendritic cells, enhancing activity, escape, immunoprophylaxis, immunotherapy, immunotoxin, kinetics, mother-to-infant transmission, mucosal immunity, neutralization, rate of progression, review, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- F105: No neutralization of primary isolates observed (John

- Moore, pers comm). (**variant cross-recognition or cross-neutralization**)
- F105: NIH AIDS Research and Reference Reagent Program: 857.
  - F105: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
  - F105: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using CD4BS MAbs F105 and IgG1b12, glycan-specific 2G12, and V3-specific 447-52D, and were unchanged. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Martín-García *et al.* [2005] (**antibody binding site definition and exposure**)
  - F105: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4BS MAbs except Fab b12 (b6, b3, F105) did not bind to either GDMR or mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
  - F105: The crystal structure of the Fab fragment from F105 was solved. It has an extended CDR H3 loop, with a Phe at the apex that may recognize the binding pocket of gp120 used by the Phe-42 residue of CD4. The potent NAB IgG1b12 recognizes an overlapping binding site, the main difference is that F105 extends across the interface of the inner and outer domains of gp120 while b12 does not. IgG1b12 also has undergone extensive affinity maturation (45 mutations) while F105 has not (13 mutations) – an average for gp120 MAbs is 22 mutations. Wilkinson *et al.* [2005] (**antibody sequence variable domain, structure**)
  - F105: The peptide 12p1 (RINNIPWSEAMM) inhibits direct binding of YU2 gp120 or Env trimer to CD4, CCR5 and MAb 17b in a concentration-dependent allosteric manner. 12p1 is thought to bind to unbound gp120 near the CD4 binding site, with a 1:1 stoichiometry. 12p1 also inhibited MAb F105 binding, presumably because F105 favors an unactivated conformation, but not MAbs 2G12 or b12. The 1:1 stoichiometry, the fact that the peptide binding site is accessible on the trimer, the non-CD4 like aspect of the binding, and an ability to inhibit viral infection in cell cultures make 12p1 a promising lead for therapeutic design. Biorn *et al.* [2004]
  - F105: NABs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. F105 was not particularly effective at neutralizing HIV-1 group O strains. Ferrantelli *et al.* [2004a] (**variant cross-recognition or cross-neutralization**)
  - F105: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
  - F105: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAB tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of CD4BS MAb F105 was decreased by trypsin, but increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
  - F105: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including F105. Pantophlet *et al.* [2004] (**vaccine antigen design**)
  - F105: The ability of F105 to neutralize R5, R5X4 and X4 primary isolates was compared to that of MAbs 17b, E51 and 412d. F105 neutralized the R5 ADA virus more efficiently than 17b, comparable to 412d, however, it neutralized R5X4 isolate 89.6 less efficiently than 412d and E51. F105 was, on the other hand, more efficient in neutralizing the X4 isolate HXBc2 than the other MAbs. Choe *et al.* [2003] (**neutralization**)
  - F105: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. F105 recognized most variants, some from each of the four individuals by gp120 immunoprecipitation. Ohagen *et al.* [2003] (**brain/CSF, variant cross-recognition or cross-neutralization**)
  - F105: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
  - F105: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-

- neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- F105: Virion capture assays are not a good predictor of neutralization, and the presentation of epitopes using this assay seems to be different from that of functional Envelope spikes on primary isolates – F105 and b6 could efficiently block the b12-mediated capture of infectious virions in a virus capture, but did not inhibit b12 neutralization – while b12 was potent at neutralizing the three primary virions JR-CSF, ADA, and 89.6, the Abs F105, 19b, and Fab b6 were overall very poor neutralizers. Poignard *et al.* [2003] (**antibody interactions**)
  - F105: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. CD4BS MAbs F105, 15e, and IgG1b12 as well as their Fab fragments inhibited CD4-independent binding of the V1/V2 loop-deleted gp120 glycoproteins of R5 HIV-1 isolates ADA, YU2 and JR-FL and to CCR5 in a concentration dependent manner. CD4BS MAbs IgG1b12, F91 and F105 and their Fab counterparts (except for C11, used as a negative control) inhibited CD4-independent JR-FL and YU-2 gp120-CCR5 binding to CCR5-expressing Cf2Th cells and syncytium formation. Raja *et al.* [2003] (**antibody binding site definition and exposure, co-receptor**)
  - F105: 17b: This paper describes the generation of CD4i MAb E51, that like CD4i MAb 17b, blocks CCR5 binding to sCD4-bound gp120. The substitutions E381R, F383S, R419D I420R, K421D, Q422L, I423S, and Y435S (HXB2 numbering) all severely reduce 17b and E51 binding. All but I423S also diminish CCR5 binding by more than 50%. The mutation F383S also inhibits sCD4 binding and F105 binding, and K421D inhibits F105 binding, but not sCD4. Xiang *et al.* [2003] (**antibody binding site definition and exposure**)
  - F105: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
  - F105: gp120 mutants were used to define the CXCR4 binding site using CXCR4 displayed on paramagnetic proteoliposomes (PMPLs) to reduce non-specific gp120 binding—basic residues in the V3 loop and the  $\beta$ 19 strand (RIKQ, positions 419-422) were involved, and deletion of the V1-V2 loops allowed CD4-independent CXCR4 binding—MAbs 17b (CD4i) and F105 (CD4BS) were used to study conformational changes in the mutants—the affinity of  $\Delta$ V1 and  $\Delta$ V1-V2 mutants for F105 was comparable to the wildtype—V3 mutants did not affect F105 binding—the K421A mutation in the  $\beta$ 19 strand dramatically reduced F105 affinity, consistent with what is known about the F105 epitope. Basmaciogullari *et al.* [2002] (**antibody binding site definition and exposure**)
  - F105: This study examined Ab interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-gp41 MAb F240 enhanced the binding of CD4BS MAbs IgG1b12 and F105 to both R5X4 and R5 isolates, but had no effect on neutralization. Anti-V3 MAb B4a1 increased CD4BS MAbs IgG1b12 and F105 to R5X4 virions, but only IgG1b12 binding was increased by B4a1 to the R5 isolate, and neutralization was not impacted. Cavacini *et al.* [2002] (**co-receptor**)
  - F105: A modified gp140 (gp140deltaCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation, retained antigenic conformational determinants as defined by binding to CD4 and to MAbs 2F5, 2G12, F105, and b12, and enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002] (**vaccine antigen design**)
  - F105: Review of NAb that notes that F105 binds the CD4BS, in combination with other MAbs it can protect some macaques against SHIV infection, and that it has strong ADCC activity. Ferrantelli & Ruprecht [2002] (**ADCC, antibody interactions, immunoprophylaxis, review**)
  - F105: HIV-1 gp160 $\delta$ CT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines—2F5 bound to gp160 $\delta$ CT with a reconstituted membrane ten-fold better than the same protein on beads, while such an affinity difference was not seen with F105 and 2G12—anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160 $\delta$ CT PLs indistinguishably from gp160 $\delta$ CT expressed on the cell surface. Grundner *et al.* [2002] (**antibody binding site definition and exposure**)
  - F105: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding and ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
  - F105: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus.

Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Ling *et al.* [2002] (**antibody binding site definition and exposure, co-receptor**)

- F105: Review of NAb that discusses mechanisms of neutralization, passive transfer of NAb and protection in animal studies, and vaccine strategies. Liu *et al.* [2002] (**immunoprophylaxis**)
- F105: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**)
- F105: Passive immunization of neonate macaques with a combination of F105+2G12+2F5 conferred complete protection against oral challenge with SHIV-vpu+ or – the combination b12+2G12+2F5 conferred partial protection against SHIV89.6 – such combinations may be useful for prophylaxis at birth and against milk born transmission – the synergistic combination of IgG1b12, 2G12, 2F5, and 4E10 neutralized a collection of HIV clade C primary isolates. Xu *et al.* [2002] (**immunoprophylaxis, mother-to-infant transmission**)
- F105: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibrin—stabilized oligomer gp140 $\delta$ 683(-FT) showed strong preferential recognition by NAb IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**vaccine antigen design**)
- F105: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**)
- F105: Mutations in two glycosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYRLINC-NTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, including to F105. Kolchinsky *et al.* [2001] (**antibody binding site definition and exposure**)
- F105: SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkeys yielded highly pathogenic SHIV KU-1—HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160—substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1—17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001] (**antibody binding site definition and exposure**)
- F105: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAb alters some step after binding. York *et al.* [2001] (**antibody binding site definition and exposure**)
- F105: A triple combination of 2F5, F105 and 2G12 effectively neutralized perinatal infection of macaque infants when challenged with SHIV-vpu+ – the plasma half-life was 7.2 +/- 2.2 days. Baba *et al.* [2000] (**immunoprophylaxis, mother-to-infant transmission**)
- F105: Host encoded intercellular adhesion molecule (ICAM-1) is incorporated by the HIV-1 virion and enhances viral infectivity – ICAM-1 does not modify virus sensitivity to antibodies 0.5beta or 4.8D or sCD4, but neutralizing ability of F105 was diminished in ICAM bearing virions in the presence of lymphocyte function-association antigen-1 (LFA-1) Ab. Fortin *et al.* [2000]
- F105: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form, although F105 was an exception and cannot neutralize either form of MN – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
- F105: A mini-review of observations of passive administration of IgG NAb conferring protection against intervenous or vaginal SHIV challenge, that considers why IgG MAbs might protect against mucosal challenge. Robert-Guroff [2000] (**immunoprophylaxis, mucosal immunity, review**)
- F105: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000] (**vaccine antigen design**)



- F105: A comparison of 25 gp120 specific, conformation dependent MAbs was done and F105 was used for competition studies – F105 did cross-compete with multiple CD4BS specific MAbs, however most could not neutralize even the autologous NL4-3 strains. Sugiura *et al.* [1999] (**antibody interactions**)
- F105: Immunoprecipitation of gp120 and gp160 expressed from a rec Semliki Forest virus by F105 and IgG1b12 indicated that the SFV expressed HIV-1 Env was folded appropriately – and SVF-HIV-1 Env vaccine gave the strongest anti-HIV-1 Env response in mice, when compared to an HIV-1 Env DNA vaccine and a rgp160 protein. Brand *et al.* [1998] (**vaccine antigen design**)
- F105: Phase I dose escalation study, single dose of 100 or 500 mg/m<sup>2</sup> was given to 4 HIV+ patients – sustained levels, no immune response against F105, no toxicity, infused Ab retained function – there was no evidence of anti-HIV-1 activity and virus was not diminished at day 1 or 7, by culture or plasma RNA. Cavacini *et al.* [1998b] (**kinetics, immunotherapy**)
- F105: The MAb F240 binds to the immunodominant region of gp41 and enhances infection in the presence of complement – reactivity of F240 is enhanced by preincubation of cells with sCD4 or anti-CD4BS MAb F105. Cavacini *et al.* [1998a] (**antibody interactions**)
- F105: Anti-C1 region MAb 87-135/9 blocks gp120 interaction with CD4+ cells – blocking activity is additive when combined with antibodies which bind in the C4 region of gp120 (F105, 388/389, and b12). Kropelin *et al.* [1998] (**antibody interactions**)
- F105: Neutralization synergy was observed when the MAbs 694/98-D (V3), 2F5 (gp41), and 2G12 (gp120 discontinuous) were used in combination, and even greater neutralizing potential was seen with the addition of a fourth MAb, F105 (CD4 BS). Li *et al.* [1998] (**antibody interactions**)
- F105: F105 enhances viral entry of viruses carrying the YU2 envelope glycoproteins, but neutralizes HXBc2. Sullivan *et al.* [1998a] (**enhancing activity**)
- F105: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998] (**antibody binding site definition and exposure, structure**)
- F105: Virus with the V1-V2 loop deleted was viable and more susceptible to neutralization by CD4i MAb 17b, and anti-V3 MAbs 1121, 9284, and 110.4, but not to a CD4BS MAb, F105 or sCD4. Cao *et al.* [1997b] (**antibody binding site definition and exposure**)
- F105: In a multilaboratory blinded study, failed to neutralize any of nine B clade primary isolates. D'Souza *et al.* [1997] (**variant cross-recognition or cross-neutralization**)
- F105: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – F105 could only achieve 50% neutralization alone – all Ab combinations tested showed synergistic neutralization – F105 has synergistic response with MAbs 694/98-D (anti-V3), 48d, 2F5, and 2G12, and also with HIVIG. Li *et al.* [1997] (**antibody interactions, variant cross-recognition or cross-neutralization**)
- F105: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- F105: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding – does not bind to HXBc2 gp120 if the 19 C-term amino acids, in conjunction with C1 positions 31-93, are deleted. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- F105: Intracellular co-expression of heavy and light chains of the Fab105 fragment MAb F105 was enhanced by inclusion of an internal ribosome entry site (IRES) sequence – the Fab105 IRES expression cassette was cloned into an adeno-associated virus (AAV) shuttle vector, and transduced into human lymphocytes which were able to produce and secrete the Fab105 fragments while maintaining normal growth – several primary HIV-1 patient isolates were effectively blocked. Chen *et al.* [1996] (**immunotherapy**)
- F105: The sulfated polysaccharide curdlan sulfate (CRDS) binds to the Envelope of T-tropic viruses and neutralizes virus – deletion of the V3 loop results in less potent inhibition of F105 binding by CRDS – binding site of F105 described as 256-257 ST, 368-370 DPE, 421 K, and 470-484 PGGGDM-RDNWRSELY. Jagodzinski *et al.* [1996] (**antibody binding site definition and exposure**)
- F105: Binding of F105 to oligomeric gp120 occurs despite the fact it cannot neutralize primary isolates. Litwin *et al.* [1996]
- F105: Neutralizes HIV-1 LAI less potently than V3 specific MAbs. McDougal *et al.* [1996]
- F105: A panel of immunotoxins were generated by linking Env MAbs to ricin A – immunotoxins mediated cell killing, but killing was not directly proportional to binding. Pincus *et al.* [1996] (**immunotoxin**)
- F105: F105 is V H4 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996] (**antibody sequence variable domain**)
- F105: Phase I study – MAb clearance in plasma has a 13 day half-life. Wolfe *et al.* [1996] (**kinetics, immunotherapy**)
- F105: Changing heavy chain from IgG1 to IgG3 increased neutralization efficiency. Cavacini *et al.* [1995]
- F105: Biotinylated F105 was used for competition studies with Ab derived from pregnant HIV-1 + women – a correlation between maternal anti-CD4 BS Abs overlapping the F105 binding site and lack of HIV-1 transmission to infants was noted. Khouri *et al.* [1995] (**mother-to-infant transmission**)
- F105: Eight patient phase Ia trial for use as an immunotherapeutic – no clinical or biochemical side effects observed, plasma levels of 10 ug/ml maintained for 21 days. Posner *et al.* [1995] (**immunotherapy**)
- F105: Efficient neutralization of T-cell adapted lines HXBc2 and MN, no neutralization of primary isolates 89.6, ADA and YU2 – even some enhancement of infection of ADA and YU2 was observed. Sullivan *et al.* [1995] (**enhancing activity, variant cross-recognition or cross-neutralization**)
- F105: An immunoassay for titrating CD4BS serum antibody was developed using a gp120-coated solid phase and competition with MAb F105 – 109/110 French HIV-1 + sera and

- 51/56 HIV-1 + African sera had detectable CD4BS Abs using this assay, demonstrating CD4 binding site conservation among diverse subtypes – CD4BS Abs were detected soon after seroconversion and persisted – 0/21 HIV-2 + sera reacted, indicating that the HIV-1 and HIV-2 CD4BS Abs are not cross-reactive. Turbica *et al.* [1995] (**assay development, subtype comparisons**)
- F105: Comparison of MAb F105 sequences with those of MAbs 21h and 15e. Bagley *et al.* [1994] (**antibody sequence variable domain**)
  - F105: Administered intravenously to four cynomolgus monkeys, plasma pharmacokinetics and biological activity tested. Cavacini *et al.* [1994b] (**kinetics**)
  - F105: Fab fragments show reduced capacity to neutralize IIIB, MN, and RF compared to intact IgG1, suggesting bivalent interaction may be important in binding and neutralization. Cavacini *et al.* [1994a] (**variant cross-recognition or cross-neutralization**)
  - F105: A human CD4+ T lymphocyte line was transduced to express Fab fragments of F105 – heavy and light chains are joined by an inter-chain linker – in the transduced cells infected with HIV-1, the Fab binds intracellularly to the envelope protein and inhibits HIV-1 production – secreted Fab fragments neutralize cell-free HIV-1 – combined intra- and extracellular binding activities of the expressed Fab make transduced cells resistant to HIV-1 infection and also can protect surrounding lymphocytes by secreting neutralizing antibodies. Chen *et al.* [1994a]; Marasco *et al.* [1993] (**variant cross-recognition or cross-neutralization**)
  - F105: MAbs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – anti-CD4 MAbs moderately inhibit gp120 binding to GalCer, possibly through steric hindrance – binding of GalCer to gp120 inhibited but did not completely block F105 binding. Cook *et al.* [1994] (**brain/CSF**)
  - F105: Used as a positive control for CD4 BS antibodies in a study of the influence of oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody binding site definition and exposure**)
  - F105: A mutation in gp41, 582 A/T, confers resistance to neutralization (also confers resistance to MAbs 48d, 21h, 15e and 17b). Thali *et al.* [1994] (**antibody binding site definition and exposure**)
  - F105: Additive MN or SF2 neutralization when combined with anti-V3 MAbs 447-52D and 257-D. Cavacini *et al.* [1993a] (**antibody interactions**)
  - F105: Serum from all asymptomatic HIV-1 positive people tested block F105 binding, but only from 27% of symptomatic individuals. Cavacini *et al.* [1993b] (**rate of progression**)
  - F105: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to a class of conformation sensitive neutralizing MAbs – required >81 fold higher concentrations to neutralize the mutant than wild type. Klasse *et al.* [1993a] (**antibody interactions**)
  - F105: Study of synergy between F105 and sera from vaccinated volunteers with V3-loop specific neutralization activity – 2/3 sera demonstrated neutralization synergy, and 3/3 binding/fusion-inhibition synergy. Montefiori *et al.* [1993] (**antibody interactions**)
  - F105: Called F-105 – neutralizes IIIB – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993]
  - F105: Ab response in IIIB lab workers was compared to gp160 LAI vaccine recipients – F105 was used as a control – infected lab workers and some of the gp160 vaccinees had a MAb response that could inhibit gp120-CD4 binding, at lower titers than the infected lab workers. Pincus *et al.* [1993] (**vaccine-specific epitope characteristics**)
  - F105: F105 binds to and neutralizes selected lab strains and 3/9 HIV-1 primary isolates – synergistic enhancement of neutralization by seropositive sera. Posner *et al.* [1993] (**antibody interactions, variant cross-recognition or cross-neutralization**)
  - F105: Study of synergy of neutralization and binding comparing F105 and sCD4 with the V3 MAbs: 50.1, 59.1, 83.1, and 58.2 – synergy was observed, and the data suggest that binding of one ligand (F105) can increase the binding of the second (e.g. V3 loop MAbs) due to conformational changes. Potts *et al.* [1993] (**antibody interactions**)
  - F105: A neutralization escape mutant (HXB2 A281V) was selected by growth of HXB2 in the presence of broadly neutralizing sera – F105 neutralization was not affected by this mutation. Watkins *et al.* [1993] (**escape**)
  - F105: Binding to Delta V1/2 and Delta V1/2/3 mutant glycoproteins is 2.4- and 13-fold greater, respectively, than binding to wildtype gp120. Wyatt *et al.* [1993] (**antibody binding site definition and exposure**)
  - F105: MAb cDNA sequence – V H4 V71-4 rearranged with a D H D-D fusion product of dlr4 and da4, and with J H5 – V kappa is from the Humvk325 germline gene joined with Jkappa 2. Marasco *et al.* [1992] (**antibody sequence variable domain**)
  - F105: F105 mediates ADCC against SF2 through the CD16+ population of PBMC – does not mediate complement-dependent cytotoxicity. Posner *et al.* [1992b] (**ADCC, complement**)
  - F105: Significant enhancement of F105 binding to RF infected cells preincubated with V3-specific MAbs V3-2 and V3-1. Posner *et al.* [1992a] (**antibody interactions**)
  - F105: Amino acid substitutions that impair F105 neutralization inhibit gp120-CD4 interaction. Thali *et al.* [1992a] (**antibody binding site definition and exposure**)
  - F105: Precipitation of Delta 297-329 env glycoprotein, which has a deleted V3 loop, is much more efficient than precipitation of wild type. Wyatt *et al.* [1992] (**antibody binding site definition and exposure**)
  - F105: First description of F105, binds topographically near the CD4-binding site – inhibits binding of free, infectious virions to uninfected HT-H9 cells, but does not react with virus adsorbed to uninfected HT-H9 cells – soluble rCD4 prebound to infected cells inhibits F105 binding – F105 inhibits infection of HT-H9 cells in standard neutralization assays with HIV-1 and MN strains. Posner *et al.* [1991] (**antibody binding site definition and exposure, antibody generation**)
  - F105: F105 neutralization escape mutants result from changes in amino acids in discontinuous regions: C2, 256-262 and C3, 386-370. Thali *et al.* [1991] (**antibody binding site definition and exposure**)

No. 1176

- MAb ID** F91 (F-91)  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)**  
**Ab Type** gp120 CD4BS  
**Research Contact** James Robinson, University of Connecticut, Storrs
- References** Pantophlet *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Raja *et al.* 2003; Pantophlet *et al.* 2003a; Kwong *et al.* 2002; Xiang *et al.* 2002b; Yang *et al.* 2002; Yang *et al.* 2000; Fouts *et al.* 1998; Binley *et al.* 1998; Parren *et al.* 1998a; Mondor *et al.* 1998; Fouts *et al.* 1997; Moore & Sodroski 1996; Moore *et al.* 1994b; Moore & Ho 1993
- Keywords** antibody binding site definition and exposure, antibody interactions, co-receptor, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization
- F91: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
  - F91: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including F91. Pantophlet *et al.* [2004] (**vaccine antigen design**)
  - F91: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
  - F91: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
  - F91: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. CD4BS

MAbs F105, 15e, and IgG1b12 as well as their Fab fragments inhibited CD4-independent binding of the V1/V2 loop-deleted gp120 glycoproteins of R5 HIV-1 isolates ADA, YU2 and JR-FL and to CCR5 in a concentration dependent manner. CD4BS MAbs IgG1b12, F91 and F105 and their Fab counterparts (except for C11, used as a negative control) inhibited CD4-independent JR-FL and YU-2 gp120-CCR5 binding to CCR5-expressing Cf2Th cells and syncytium formation. Raja *et al.* [2003] (**co-receptor**)

- F91: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
- F91: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- F91: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure**)
- F91: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif de-

rived from T4 bacteriophage fibrin – stabilized oligomer gp140 delta683(-FT) showed strong preferential recognition by NAb IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MABs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**antibody binding site definition and exposure**)

- F91: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MABs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MABs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MABs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000] (**antibody binding site definition and exposure**)
- F91: A panel of MABs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – CD4BS MABs 15e, F91 and IgG1b12 bound better to the deleted protein than to wild type. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
- F91: CD4BS MABs 15e, 21h, and F91 bind with even lower affinity than 205-43-1 and 205-42-15 to JRFL oligomer – conclusions of this paper contrast with Parren *et al.* [1998a] Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- F91: Weak inhibition of binding of Hx10 to CD4 positive or negative cells, weakly neutralizing. Mondor *et al.* [1998]
- F91: The MAB and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- F91: Study shows neutralization is not predicted by MAB binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – F91 bound monomer, did not bind oligomer or neutralize JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
- F91: Unusual pattern of reciprocal enhancement with several anti-V2 and V3 directed MABs – reciprocal inhibition of other CD4BS MABs. Moore & Sodroski [1996] (**antibody binding site definition and exposure, antibody interactions**)
- F91: Has strong cross-reactivity with gp120 monomers from most subtypes, A-F. Moore *et al.* [1994b] (**subtype comparisons**)
- F91: Called F-91 – neutralizes IIIB – reactive with SF-2 gp120 – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993] (**variant cross-recognition or cross-neutralization**)

No. 1177

MAB ID FG39

**HXB2 Location** Env  
**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Zwick *et al.* 2003

**Keywords** antibody interactions

- FG39: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MABs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MABs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MABs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4BS Fab first used in this study. Zwick *et al.* [2003] (**antibody interactions**)

No. 1178

MAB ID Fbb14

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Zwick *et al.* 2003

**Keywords** antibody interactions

- Fbb14: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MABs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MABs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MABs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4BS Fab first used in this study. Fbb14 was unusual among CD4BS Abs in that it didn't enhance 4KG5's binding, like b12, but it did not inhibit it either as the other 13 CD4BS Abs did, it remained neutral. Zwick *et al.* [2003] (**antibody interactions**)

No. 1179

MAB ID GP13 (ARP3054)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1)

**Ab Type** gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Vella *et al.* 2002; Schutten *et al.* 1997; Schutten *et al.* 1996; Wisnewski *et al.* 1996; Bolmstedt *et al.* 1996; Schutten *et al.* 1995b; Schutten *et al.* 1995a; Bagley *et al.* 1994; Back *et al.* 1993; Schutten *et al.* 1993

**Keywords** antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, assay development, binding affinity, enhancing activity, escape, review, subtype comparisons, variant cross-recognition or cross-neutralization

- GP13: UK Medical Research council AIDS reagent: ARP3054.
- GP13: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- GP13: Called ARP3054: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs. Vella *et al.* [2002] (**assay development**)
- GP13: Neutralized (50%) an SI-env chimeric virus and enhanced (>5 fold) an NSI-env chimeric virus. Schutten *et al.* [1997] (**enhancing activity, variant cross-recognition or cross-neutralization**)
- GP13: Sera were obtained from guinea pigs vaccinated either with gp160, or with gp160 lacking N-linked glycans at N406, N448, and N463 – these sera could block equally well both the CD4 BS MAb GP13 and the V3 MAb F58/H3. Bolmstedt *et al.* [1996] (**antibody interactions**)
- GP13: IIIB neutralizing MAbs *in vitro* fail to neutralize in a mouse model *in vivo*. Schutten *et al.* [1996]
- GP13: GP13 is V H5 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- GP13: Neutralizes IIIB – only slight inhibition of SI phenotype, and strong enhancement of NSI phenotype chimeric viruses, that incorporated different envs from the same donor. Schutten *et al.* [1995a] (**enhancing activity, variant cross-recognition or cross-neutralization**)
- GP13: Neutralizes T-cell adapted viruses but not the SI strain 16.2, despite high binding affinity. Schutten *et al.* [1995b] (**variant cross-recognition or cross-neutralization, binding affinity**)
- GP13: Mutations in a neutralization resistant isolate obtained by passage of the IIIB isolate in chimpanzees reduced neutralization, but the escape was not as clear as seen with anti-V3 MAbs. Back *et al.* [1993] (**escape**)
- GP13: Neutralized a broad range of HIV-1 strains from phylogenetically different subfamilies – the following gp120 amino acid substitutions strongly inhibit binding: 256(S/Y), 257(T/G), 262(N/T), 368(D/R or K), 370(E/R or Q or D), 384(Y/E). Schutten *et al.* [1993] (**antibody binding site definition and exposure, subtype comparisons**)

**No.** 1180  
**Mab ID** GP44  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**

**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1)  
**Ab Type** gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Wisnewski *et al.* 1996; Bagley *et al.* 1994; Schutten *et al.* 1993

**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, review, variant cross-recognition or cross-neutralization

- GP44: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- GP44: GP44 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisnewski *et al.* [1996] (**antibody sequence variable domain**)
- GP44: Exhibited a more restricted pattern of neutralizing activity than GP13 and GP68 – the following gp120 amino acid substitutions strongly inhibit binding: 256(S/Y), 257(T/G), 262(N/T), 368(D/R or K), 370(E/R or Q or D) Schutten *et al.* [1993] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)

**No.** 1181  
**Mab ID** GP68  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**

**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1)  
**Ab Type** gp120 CD4BS

**References** Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Guillon *et al.* 2002b; Wisnewski *et al.* 1996; Schutten *et al.* 1995a; Bagley *et al.* 1994; Klasse *et al.* 1993a; Schutten *et al.* 1993

**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, dendritic cells, enhancing activity, neutralization, review, variant cross-recognition or cross-neutralization

- GP68: UK Medical Research Council AIDS reagent: ARP3055.
- GP68: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- GP68: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)

- GP68: The affect of Ab binding on infectivity was studied by pseudotyping three related envs with different phenotypes – R5 viruses were preferentially enhanced, not X4 – the V3 region was the main determinant of Ab-mediated enhancement and modulation of the interaction between CCR5 and gp120 is critical – tests with MAbs anti-V3 391/95-D and CD4BS-specific GP68 indicate that Ab specificity did not determine whether or not infectivity was enhanced or neutralized, rather the phenotype was determined by Envelope conformation. Guillon *et al.* [2002b] (**enhancing activity, variant cross-recognition or cross-neutralization**)
- GP68: GP68 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996] (**antibody sequence variable domain**)
- GP68: Neutralizes IIIB – only slight inhibition of SI phenotype, and strong enhancement of NSI phenotype chimeric viruses, that incorporated different envs from the same donor. Schutten *et al.* [1995a] (**variant cross-recognition or cross-neutralization**)
- GP68: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to a class of conformation sensitive neutralizing MAbs – GP68 required markedly higher concentrations to neutralize the mutant than wild type. Klasse *et al.* [1993a] (**antibody binding site definition and exposure**)
- GP68: Neutralized a broad range of HIV-1 lab strains from phylogenetically different subfamilies – the following gp120 amino acid substitutions strongly inhibit binding: 117(K/W), 256(S/Y), 257(T/G), 262(N/T), 368(D/R or K), 370(E/R or Q), 384(Y/E), 435(Y/H) Schutten *et al.* [1993] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)

No. 1182

MAB ID HF1.7

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing L

Immunogen anti-idiotype

Species (Isotype) mouse (IgM)

Ab Type gp120 CD4BS

References Chanh *et al.* 1987

- HF1.7: An anti-Id antibody stimulated by anti-CD4 MAB Leu-3a binds to recombinant gp160, suggesting HF1.7 mimics CD4. Chanh *et al.* [1987]

No. 1183

MAB ID HT5 (205-43-1)

HXB2 Location Env

Author Location gp120

Epitope

Subtype B

Neutralizing L (weak)

Immunogen HIV-1 infection

Species (Isotype) human

Ab Type gp120 CD4BS

Research Contact Ciba-Geigy AG (Basel, Switzerland), and Tanox Biosystems, Houston, Texas

**References** Pugach *et al.* 2004; Gorny & Zolla-Pazner 2004; Herrera *et al.* 2003; Grovit-Ferbas *et al.* 2000; Parren *et al.* 1998a; Fouts *et al.* 1998; Fouts *et al.* 1997; Moore *et al.* 1995a; Moore *et al.* 1994b

**Keywords** antibody binding site definition and exposure, antibody interactions, binding affinity, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization, viral fitness and reversion

- HT5: Also called 205-43-1. This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAB, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- HT5: Called 205-43-1: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. Three CD4BS MAbs, 205-46-9, 205-42-15, and 205-43-1, did not neutralize either the primary or passaged variant. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization, viral fitness and reversion**)
- HT5: Called 205-43-1 – CD4BS MAbs b12 (neutralizing) and 205-42-15, 204-43-1, 205-46-9 (nonneutralizing) all cross-competed for binding to monomeric gp120, indicating the topological proximity of their epitopes, however, the nonneutralizing CD4BS MAbs did not interfere with the neutralization activity of MAb b12 – the nonneutralizing MAbs partially competed with b12 for Env binding of the surface of Env-transfected cells – this suggests Env has two categories of binding site for CD4BS MAbs, one recognized by both b12 and nonneutralizing CD4BS MAbs, the other is recognized by only b12 – Ab-gp120 interactions based on the use of monomeric gp120 or Env-transfected cells do not predict the outcome of HIV-1 neutralization assays, and they should be interpreted with caution. Herrera *et al.* [2003] (**antibody binding site definition and exposure, antibody interactions**)
- HT5: Called 205-43-1: To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**antibody binding site definition and exposure, vaccine antigen design**)
- HT5: HT5, HT6, and HT7 are also known as 205-43-1, 205-42-15, and 205-46-9, respectively. Rank order of CD4BS antibodies oligomer binding is IgG1b12 = 2G6 = 205-46-9 > 205-43-1 = 205-42-15 > 15e = 21h = F91, and the only thing notably distinguishing about neutralizing IgG1b12 is that it depends on residues in V2. Fouts *et al.* [1998] (**binding affinity**)

- HT5: HT5 and HT6 bind JRSF oligomer but with low affinity, and are not neutralizing – conclusions of this paper contrast with Parren *et al.* [1998a] Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- HT5: MAbs IgG1b12, HT5, HT6, and HT7 cross-compete for binding to monomeric gp120, bind equally well, inhibit gp120-sCD4 interactions, but only IgG1b12 neutralizes JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure, antibody interactions**)
- HT5: Despite highly cross-reactive binding to many primary and T-cell adapted viral strains, only weakly neutralizes IIIB and MN. Moore *et al.* [1995a] (**variant cross-recognition or cross-neutralization**)
- HT5: 205-46-9 was cross-reactive across clades A-F, 205-43-1 very cross-reactive but not quite as extensive 205-46-9. Moore *et al.* [1994b] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1184

**MAb ID** HT6 (205-42-15)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L (weak)

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**Research Contact** Ciba-Geigy AG Basel, Switzerland, and Tanox Biosystems, Houston, Texas

**References** Pugach *et al.* 2004; Gorny & Zolla-Pazner 2004; Herrera *et al.* 2003; Parren *et al.* 1998a; Fouts *et al.* 1998; Fouts *et al.* 1997; Moore *et al.* 1995a; Moore *et al.* 1994b

**Keywords** antibody binding site definition and exposure, antibody interactions, review, subtype comparisons, variant cross-recognition or cross-neutralization, viral fitness and reversion

- HT6: Called 205-42-15: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- HT6: Called 205-42-15: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. Three CD4BS MAbs, 205-46-9, 205-42-15, and 205-43-1, did not neutralize either the primary or passaged variant. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization, viral fitness and reversion**)
- HT6: Called 205-42-15: CD4BS MAbs b12 (neutralizing) and 205-42-15, 204-43-1, 205-46-9 (nonneutralizing) all cross-competed for binding to monomeric gp120, indicating the

topological proximity of their epitopes, however, the nonneutralizing CD4BS MAbs did not interfere with the neutralization activity of MAb b12 – the nonneutralizing MAbs partially competed with b12 for Env binding of the surface of Env-transfected cells – this suggests Env has two categories of binding site for CD4BS MAbs, one recognized by both b12 and nonneutralizing CD4BS MAbs, the other is recognized by only b12 – Ab-gp120 interactions based on the use of monomeric gp120 or Env-transfected cells do not predict the outcome of HIV-1 neutralization assays, and they should be interpreted with caution. Herrera *et al.* [2003] (**antibody binding site definition and exposure, antibody interactions**)

- HT6: HT5, HT6, and HT7 are also known as 205-43-1, 205-42-15, and 205-46-9, respectively. Fouts *et al.* [1998]
- HT6: HT5 and HT6 bind JRSF oligomer but with low affinity, and are not neutralizing – conclusions of this paper contrast with Parren *et al.* [1998a] Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- HT6: MAbs IgG1b12, HT5, HT6, and HT7 cross-compete for binding to monomeric gp120, bind equally well, inhibit gp120-sCD4 interactions, but only IgG1b12 neutralizes JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure, antibody interactions**)
- HT6: Despite highly cross-reactive binding to many primary and T-cell adapted viral strains, only weakly neutralizes IIIB and MN. Moore *et al.* [1995a] (**variant cross-recognition or cross-neutralization**)
- HT6: 205-46-9 was cross-reactive across clades A-F, 205-43-1 was not quite as extensively cross-reactive. Moore *et al.* [1994b] (**subtype comparisons**)

No. 1185

**MAb ID** HT7 (205-46-9)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L (IIIB)

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**Research Contact** Ciba-Geigy AG (Basel, Switzerland), and Tanox Biosystems, Houston, Texas

**References** Pugach *et al.* 2004; Gorny & Zolla-Pazner 2004; Herrera *et al.* 2003; Grovit-Ferbas *et al.* 2000; Parren *et al.* 1998a; Fouts *et al.* 1998; Fouts *et al.* 1997; Moore *et al.* 1995a; Moore *et al.* 1994b

**Keywords** antibody binding site definition and exposure, assay standardization/improvement, review, subtype comparisons, variant cross-recognition or cross-neutralization, viral fitness and reversion

- HT7: Also called 205-46-9. This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- HT7: Called 205-46-9: A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes

in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. Three CD4BS MAbs, 205-46-9, 205-42-15, and 205-43-1, did not neutralize either the primary or passaged variant. Pugach *et al.* [2004] (**variant cross-recognition or cross-neutralization, viral fitness and reversion**)

- HT7: Called 205-46-9 – CD4BS MAbs b12 (neutralizing) and 205-42-15, 204-43-1, 205-46-9 (nonneutralizing) all cross-competed for binding to monomeric gp120, indicating the topological proximity of their epitopes, however, the nonneutralizing CD4BS MAbs did not interfere with the neutralization activity of MAb b12 – the nonneutralizing MAbs partially competed with b12 for Env binding of the surface of Env-transfected cells – this suggests Env has two categories of binding site for CD4BS MAbs, one recognized by both b12 and nonneutralizing CD4BS MAbs, the other is recognized by only b12 – Ab-gp120 interactions based on the use of monomeric gp120 or Env-transfected cells do not predict the outcome of HIV-1 neutralization assays, and they should be interpreted with caution. Herrera *et al.* [2003] (**antibody binding site definition and exposure**)
- HT7: Called 205-46-9. To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**antibody binding site definition and exposure**)
- HT7: Called 205-46-9. HT5, HT6, and HT7 are also known as 205-43-1, 205-42-15, and 205-46-9, respectively. Binds JRSF oligomer with high affinity as does IgG1b12, but IgG1b12 is neutralizing, 205-46-9 is not – conclusions of this paper contrast with Parren98 – authors propose a model where 205-46-9 and 2G6 may inhibit CD4 binding, but cause a conformational shift which enhances CCR5 binding and thus counteracts the neutralizing effect – rank order of CD4BS antibodies oligomer binding is IgG1b12 = 2G6 = 205-46-9 > 205-43-1 = 205-42-15 > 15e = 21h = F91, and the only thing notably distinguishing about neutralizing IgG1b12 is that it depends on residues in V2. Fouts *et al.* [1998] (**assay standardization/improvement**)
- HT7: Binds JRSF oligomer with high affinity, at least as high as IgG1b12, but IgG1b12 is neutralizing, H7 is not – conclusions of this paper contrast with Parren *et al.* [1998a] – authors propose a model where H7 may inhibit CD4 binding, but cause a conformational shift which enhances CCR5 binding and thus counteracts the neutralizing effect Fouts *et al.* [1998]. Fouts *et al.* [1998]; Parren *et al.* [1998a] (**antibody binding site definition and exposure**)
- HT7: MAbs IgG1b12, HT5, HT6, and HT7 cross-compete for binding to monomeric gp120, bind equally well, inhibit gp120-sCD4 interactions, but only IgG1b12 neutralizes JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)

- HT7: Despite highly cross-reactive binding to many primary and T-cell adapted viral strains, only neutralizes IIIB well, with sporadic weak neutralization of other isolates. Moore *et al.* [1995a] (**variant cross-recognition or cross-neutralization**)
- HT7: 205-46-9 was cross-reactive across clades A-F, 205-43-1 was cross-reactive, but not quite as extensive. Moore *et al.* [1994b] (**subtype comparisons**)

No. 1186

Mab ID ICR 39.13g (ICR39.13g, 39.13g, ICR39.13)

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing L

Immunogen vaccine

Vector/Type: protein Strain: B clade BH10

HIV component: gp120

Species (Isotype) rat (IgG2b)

Ab Type gp120 CD4BS

Research Contact Jackie Cordell and C. Dean

References Holl *et al.* 2006a; Vella *et al.* 2002; Peet *et al.* 1998; Klasse & Sattentau 1996; Armstrong & Dimmock 1996; McKeating *et al.* 1996; Beretta & Dalgleish 1994; McLain & Dimmock 1994; Klasse *et al.* 1993a; Thali *et al.* 1993; Moore & Ho 1993; McKeating *et al.* 1993b; McKeating *et al.* 1992c; McKeating *et al.* 1992a; Cordell *et al.* 1991

Keywords dendritic cells, neutralization

- ICR 39.13g: UK Medical Research Council AIDS reagent: ARP390.
- ICR39.13: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- ICR 39.13g: Called ARP390/391, but no such entry was found at the UK Medical Research Council AIDS reagent web site: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs. Vella *et al.* [2002]
- ICR 39.13g: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind – ICR 39.13g was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]
- ICR 39.13g: Post-attachment neutralization mechanism, in contrast to MAb 39.3b. Armstrong & Dimmock [1996]
- ICR 39.13g: Variants of LAI have differing neutralization susceptibility to 39.13g. Klasse & Sattentau [1996]
- ICR 39.13g: Called 39.13g Neutralizes HXB2, but fails to neutralize chimeric virus with gp120 from primary isolates in an HXB2 background. McKeating *et al.* [1996]



- ICR 39.13g: Kinetics of neutralization studied – no lag for 39.3b, while ICR 39.13g and ICR 41.1i have lags of 5 and 15 min respectively – mediates neutralization with 2.3 molecules of IgG. McLain & Dimmock [1994]
- ICR 39.13g: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to a class of conformation sensitive neutralizing MAbs – ICR 39.13g required moderately higher concentrations to neutralize the mutant than wild type. Klasse *et al.* [1993a]
- ICR 39.13g: Neutralization activity against HXB10, RF, SF-2 and MN strains of HIV-1. McKeating *et al.* [1993b]
- ICR 39.13g: Conformational, does not bind denatured gp120 – weak neutralization of IIIB – strong inhibition of HIV+ human sera binding to IIIB gp120. Moore & Ho [1993]
- ICR 39.13g: Strongly inhibits CD4 inducible MAb 48d. Thali *et al.* [1993]
- ICR 39.13g: Binds to a conformational epitope involved in CD4 binding – exerts a synergistic effect in combination with V3 directed MAbs. McKeating *et al.* [1992a]
- ICR 39.13g: Cross-competes with MAbs ICR 39.3b and 15e. Cordell *et al.* [1991]

No. 1187

**MAb ID** ICR 39.3b (39.3, 39.3b, ICR39.3b)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120

**Species (Isotype)** rat (IgG2b)

**Ab Type** gp120 CD4BS

**Research Contact** J. Cordell and C. Dean

**References** Wyatt *et al.* 1998; Jeffs *et al.* 1996; Armstrong & Dimmock 1996; McLain & Dimmock 1994; Moore *et al.* 1993b; Moore & Ho 1993; McKeating *et al.* 1992c; Cordell *et al.* 1991

- ICR 39.3b: UK Medical Research Council AIDS reagent: ARP391.
- ICR 39.3b: Called 39.3 – summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding. Wyatt *et al.* [1998]
- ICR 39.3b: Neutralizes only if the antibody is added prior to the attachment of the virus to the cell, in contrast to 39.13g. Armstrong & Dimmock [1996]
- ICR 39.3b: Called 39.3b – increased binding when V1/V2 or V1/V2 and V3 were deleted from gp120. Jeffs *et al.* [1996]
- ICR 39.3b: Kinetics of neutralization studied – no lag for 39.3b, while ICR 39.13g and ICR 41.1i have lags of 5 and 15 min respectively. McLain & Dimmock [1994]
- ICR 39.3b: Conformational, does not bind to denatured IIIB. Moore & Ho [1993]
- ICR 39.3b: Cross-competes with MAbs ICR 39.13g and 15e. Cordell *et al.* [1991]

No. 1188

**MAb ID** Ia3

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Zwick *et al.* 2003

**Keywords** antibody interactions

- Ia3: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4BS Fab first used in this study. Zwick *et al.* [2003] (**antibody interactions**)

No. 1189

**MAb ID** Ia7

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Zwick *et al.* 2003

**Keywords** antibody interactions

- Ia7: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4BS Fab first used in this study. Zwick *et al.* [2003] (**antibody interactions**)

No. 1190

**MAb ID** IgG1b12 (Fab b12, Fab 3B3, MAb IgG1b12, IgG1-b12, IgG1 b12, IgGB12, b4/12)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Subtype** B

**Neutralizing** L P

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 CD4BS

**Research Contact** D. Burton, Scripps Research Institute, La Jolla, CA, also J. Geltowsky and J. Pyati, R. W. Johnson Pharmaceutical Resear

**References** Franke *et al.* 2006; Gray *et al.* 2006; Braibant *et al.* 2006; Davis *et al.* 2006; Cham *et al.* 2006; Choudhry *et al.* 2006; Holl *et al.* 2006a; Jiang *et al.* 2006; Herrera *et al.* 2006; Quakkelaar *et al.* 2007; Pantophlet *et al.* 2007; Law *et al.* 2007; Kraft *et al.* 2007; Huang *et al.* 2007a; Honnen *et al.* 2007; Haim *et al.* 2007; Bowley *et al.* 2007; Kothe *et al.* 2007; Ferrantelli *et al.* 2007; Dimitrov *et al.* 2007; Dhillon *et al.* 2007; Dey *et al.* 2007; Choudhry *et al.* 2007; Blish *et al.* 2007; Billington *et al.* 2007; Liao *et al.* 2006; Haynes & Montefiori 2006; Holl *et al.* 2006b; Zipeto *et al.* 2005; Wilkinson *et al.* 2005; Selvarajah *et al.* 2005; Ren *et al.* 2005; Raviv *et al.* 2005; Pinter *et al.* 2005; Martín-García *et al.* 2005; Lusso *et al.* 2005; Luo *et al.* 2006; Krachmarov *et al.* 2005; Heap *et al.* 2005a; Haynes *et al.* 2005; Gorny *et al.* 2005; Chen *et al.* 2005; Safrit *et al.* 2004; Pugach *et al.* 2004; Pinter *et al.* 2004; Pantophlet *et al.* 2004; Nabatov *et al.* 2004; McCaffrey *et al.* 2004; Jeffs *et al.* 2004; Ferrantelli *et al.* 2004a; Dacheux *et al.* 2004; Biorn *et al.* 2004; Binley *et al.* 2004; Zwick *et al.* 2004; Zwick *et al.* 2003; Pantophlet *et al.* 2003b; Zhu *et al.* 2003; Veazey *et al.* 2003; Montefiori *et al.* 2003; Kitabwalla *et al.* 2003; Zhang *et al.* 2003; Wang 2003; Mascola 2003; Raja *et al.* 2003; Hart *et al.* 2003; Ferrantelli *et al.* 2003; Dey *et al.* 2003; Cavacini *et al.* 2003; Binley *et al.* 2003; Herrera *et al.* 2003; Pantophlet *et al.* 2003a; Poignard *et al.* 2003; Ling *et al.* 2002; Lewis *et al.* 2002; Kwong *et al.* 2002; Gorry *et al.* 2002; Cavacini *et al.* 2002; Bures *et al.* 2002; Liu *et al.* 2002; Ferrantelli & Ruprecht 2002; Klasse & Sattentau 2002; Zhang *et al.* 2002; Grundner *et al.* 2002; Edwards *et al.* 2002; Xiang *et al.* 2002b; Vella *et al.* 2002; Chakrabarti *et al.* 2002; Xu *et al.* 2002; Scanlan *et al.* 2002; Sapphire *et al.* 2002; Yang *et al.* 2002; Schulke *et al.* 2002; Sanders *et al.* 2002; Golding *et al.* 2002b; Srivastava *et al.* 2002; Hezareh *et al.* 2001; Xu *et al.* 2001; Hofmann-Lehmann *et al.* 2001; Verrier *et al.* 2001; Spenlehauer *et al.* 2001; Zeder-Lutz *et al.* 2001; Poignard *et al.* 2001; Parren *et al.* 2001; Zwick *et al.* 2001c; Zwick *et al.* 2001b; Zwick *et al.* 2001a; York *et al.* 2001; Yang *et al.* 2001; Sapphire *et al.* 2001b; Sapphire *et al.* 2001a; Kolchinsky *et al.* 2001; Si *et al.* 2001; Park *et al.* 2000; Nyambi *et al.* 2000; Ly & Stamatatos 2000; Grovit-Ferbas *et al.* 2000; Binley *et al.* 1999; Beddows *et al.* 1999; Giraud *et al.* 1999; Montefiori & Evans

1999; Hioe *et al.* 1999; Jackson *et al.* 1999; Crawford *et al.* 1999; Poignard *et al.* 1999; Stamatatos & Cheng-Mayer 1998; Kropelin *et al.* 1998; Frankel *et al.* 1998; Sullivan *et al.* 1998a; Schonning *et al.* 1998; Brand *et al.* 1998; Parren *et al.* 1998b; Takefman *et al.* 1998; Fouts *et al.* 1998; Binley *et al.* 1998; Connor *et al.* 1998; Parren *et al.* 1998a; Mondor *et al.* 1998; Wyatt *et al.* 1998; Valenzuela *et al.* 1998; Parren & Burton 1997; Parren *et al.* 1997a; Parren *et al.* 1997b; Boots *et al.* 1997; Burton & Montefiori 1997; Wyatt *et al.* 1997; Ugolini *et al.* 1997; Ditzel *et al.* 1997; Stamatatos *et al.* 1997; Moore & Trkola 1997; Kessler II *et al.* 1997; Li *et al.* 1997; Fouts *et al.* 1997; Mo *et al.* 1997; Schutten *et al.* 1997; D'Souza *et al.* 1997; McKeating 1996; Sattentau 1996; Trkola *et al.* 1996a; Poignard *et al.* 1996a; Poignard *et al.* 1996b; Gauduin *et al.* 1996; Moore & Sodroski 1996; Yang *et al.* 1997c; Sullivan *et al.* 1995; Ditzel *et al.* 1995; Trkola *et al.* 1995; Parren *et al.* 1995; Moore & Ho 1995; Moore *et al.* 1995a; Sattentau 1995; Sattentau *et al.* 1995; Kessler *et al.* 1995; Moore *et al.* 1994b; Burton *et al.* 1994; Roben *et al.* 1994; Barbas III *et al.* 1992; Burton *et al.* 1991

**Keywords** acute/early infection, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, assay standardization/improvement, binding affinity, co-receptor, complement, dendritic cells, enhancing activity, escape, immunoprophylaxis, immunotherapy, kinetics, mimics, mimotopes, mother-to-infant transmission, mucosal immunity, neutralization, responses in children, review, structure, subtype comparisons, therapeutic vaccine, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- IgG1b12 database comment: Fab b12 was derived from IgG1b12, Fab 3B3 was derived from Fab b12 by random mutagenesis and selected for increased affinity to sgp120. (**antibody generation**)
- IgG1b12: UK Medical Research Council AIDS reagent: ARP3065.
- IgG1b12: NIH AIDS Research and Reference Reagent Program: 2640.
- IgG1b12: This Ab was found to be able to bind to a highly stable trimeric rgp140 derived from a HIV-1 subtype D isolate containing intermonomer V3-derived disulfide bonds and lacking gp120/gp41 cleavage. Billington *et al.* [2007]
- IgG1b12: Only 1/15 subtype A HIV-1 envelopes from samples taken early in infection was neutralized by b12; the SF162 Env control was neutralized as expected. Blish *et al.*

- [2007] (**neutralization, acute/early infection, subtype comparisons**)
- IgG1b12: Yeast display was compared to phage display and shown to select all the scFv identified by phage display and additional novel antibodies. This MAb was used in a competition assays to determine the binding region of the MAbs selected from the yeast displayed antibody library. Bowley *et al.* [2007]
  - IgG1b12: This MAb was used in a binding competitive assay to approximately localize epitopes for neutralizing MAbs m22, m24 and m46. It competed against m22 and m24 but not m46. Choudhry *et al.* [2007] (**antibody interactions**)
  - IgG1b12: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP trimers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. Dey *et al.* [2007] (**therapeutic vaccine**)
  - IgG1b12: Polyclonal IgGs from broadly neutralizing sera from two clade B and one clade A infected asymptomatic individuals were able to efficiently inhibit binding of b12 to the WT gp120 but not to the hyperglycosylated mutant gp120, which does not bind conventional nonneutralizing CD4BS Abs but retains binding of b12. This suggests that any CD4BS Abs present in the sera from the three patients responsible for broad neutralization must recognize the CD4BS somewhat differently than b12. This Ab was used to help define the antigenic profile of envelopes used in serum depletion experiments to attempt to define the neutralizing specificities of broadly cross-reactive neutralizing serum; it bound to JR-FL and JR-CSF gp120 monomers and to a lesser extent to core JR-CSF gp120 monomer used in the same experiments. Dhillon *et al.* [2007] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - IgG1b12: Inhibition kinetics experiments with this Ab showed that after 60 min of incubation of virus and cells, with b12 there was nearly 100% infection, indicating that all of the Envs had escaped inhibition by b12 by attaching to CD4 molecules. This was about 20 min earlier than escape of inhibition by 2F5 and 4E10. Dimitrov *et al.* [2007] (**antibody binding site definition and exposure, neutralization, kinetics**)
  - IgG1b12: Newborn macaques were challenged orally with the highly pathogenic SHIV89.6P and then treated intravenously with a combination of IgG1b12, 2G12, 2F5 and 4E10 one and 12 hours post-virus exposure. All control animals became highly viremic and developed AIDS. In the group treated with mAbs 1 hour post-virus exposure, 3/4 animals were protected from persistent systemic infection and one was protected from disease. In the group treated with mAbs 12 hour post-virus exposure, one animal was protected from persistent systemic infection and disease was prevented or delayed in two animals. IgG1b12, 2G12, and 4E10 were also given 24 hours after exposure in a separate study; 4/4 treated animals become viremic, but with delayed and lower peak viremia relative to controls. 3/4 treated animals did not get AIDS during the follow up period, and 1 showed a delayed progression to AIDS, while the 4 untreated animals died of AIDS. Thus the success of passive immunization with NAbs depends on the time window between virus exposure and the start of immunoprophylaxis. Ferrantelli *et al.* [2007] (**immunoprophylaxis**)
  - IgG1b12: The binding of b12, 2F5 and 2G12 to the cell-free virus interferes with a step of infection subsequent to cell attachment. HIV escape from b12 occurred 30 and 10 min before escape from 2F5 for IIIB infection of HeLa cells and JRFL infection of Cf2Th-CD4/CCR5 cells, respectively, indicating that neutralization efficiency is determined by the time frames during which Ab can bind to the receptor-activated envelope proteins during the entry phase. b12 cell-free virus neutralization was initiated immediately after exposure to the antibody. Haim *et al.* [2007] (**kinetics**)
  - IgG1b12: The neutralizing activity of this antibody for the JR-FL Env variant with the N160K/E160K mutations was measured in comparison with the neutralizing activity of 2909, which was found to be higher. Honnen *et al.* [2007] (**neutralization**)
  - IgG1b12: Binding of IgG1b12 to envelope glycoprotein was significantly increased in the presence of a small molecule HIV-1 entry inhibitor, IC9564, suggesting that the inhibitor changed the conformation of gp120 so that that reacted better with IgG1b12. IC9564 also induces conformational change of gp120 to allow the CD4i antibody 17b to bind, but inhibits CD4-induced gp41 conformational changes. Huang *et al.* [2007a] (**antibody binding site definition and exposure**)
  - IgG1b12: IgG1b12: Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 co-receptor. These constructs were sensitive to neutralization by a panel of patient plasma and neutralizing MAbs. The B consensus envelopes were sensitive to neutralization by IgG1b12 except the one with the removed glycosylation site at the base of the V1V2 loop, and an Env derived from a patient during early infection. In contrast, truncation of the gp41 cytoplasmic domain (gp145) yielded the Env that was the most sensitive to IgG1b12. Kothe *et al.* [2007] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)
  - IgG1b12: Viruses from 304 days and at 643 days (time of death) post-infection of a macaque infected with SHIV SF162P4 were resistant to contemporaneous serum that had broadly reactive NAbs. SF162 was sensitive to neutralization by b12, but the viral isolates evolved to become increasingly resistant. Kraft *et al.* [2007] (**neutralization, escape**)
  - gG1b12: Inhibition of b12 binding to gp120 by b12-like Abs in sera from long-term non-progressors (LTNP) was determined. It was shown that large amounts of b12-like Abs were present in all sera from LTNPs, however, no statistically significant correlation was found for the specificity of this Ab comparing sera able to neutralize all four HIV-1 strains and sera that could not. Braibant *et al.* [2006] (**enhancing ac-**

- tivity, neutralization, variant cross-recognition or cross-neutralization, subtype comparisons)**
- IgG1b12: Cloned Envs (clades A, B, C, D, F1, CRF01\_AE, CRF02\_AG, CRF06\_cpx and CRF11\_cpx) derived from donors either with or without broadly cross-reactive neutralizing antibodies were shown to be of comparable susceptibility to neutralization by IgG1b12. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
  - IgG1b12: Neutralization of HIV-1 primary isolates of different HIV-1 clades (A, B, C, D, E) by b12 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 and CCR5 cell surface concentration had no significant effect on the inhibitory activity of this Ab. Choudhry *et al.* [2006] (**co-receptor, neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
  - IgG1b12: Neutralization rates and rate constants for the neutralization of clade B primary isolates SF33, SF162 and 89.6 by this Ab were determined. All isolates were neutralized but with different kinetics. It was shown that neutralization sensitivity is not associated with neutralization of cell-associated or free virus. Davis *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, kinetics**)
  - b12: Inhibition of gp120 interaction with this Ab by a synthesized scaffolded peptide containing three fragments making up the binding site of gp120 for CD4 was determined. The inhibition activity of the three fragments separately was also determined. It was shown that none of the individual peptides were able to inhibit the b12-gp120 interaction but the scaffolded peptide did, indicating a synergistic effect of combining all three fragments in one molecule. Franke *et al.* [2006] (**mimics**)
  - gG1b12: Env-pseudotyped viruses were constructed from the gp160 envelope genes from seven children infected with subtype C HIV-1. IgG1b12 neutralized four of the seven viruses and the clade B control. When this Ab was mixed with 2G12 and 2F5, the neutralization was similar as to IgG1b12 alone, indicating that the majority of the pool activity was due to this Ab. When 4E10 was added to this mix, all isolates were neutralized. Gray *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, responses in children, mother-to-infant transmission**)
  - IgG1b12: This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure, enhancing activity**)
  - IgG1b12: Viruses with cleavage-competent 2G12-knockout Env and cleavage-defective Env able to bind 2G12 were constructed. Env pseudotyped virions bearing either Wt3.2P(+)-gp140 $\delta$ ct Env or a mixture of the wildtype and cleavage-defective Env had similar sensitivities to neutralization by b12. The neutralization by b12 was unaffected by 2G12 binding to uncleaved Env suggesting that only binding to cleavage-competent homotrimers is relevant to neutralization. Herrera *et al.* [2006] (**neutralization, binding affinity**)
  - IgG1b12: Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in immature monocyte-derived dendritic cells (iMDDCs) was evaluated. It was shown that HIV neutralizing activity of IgG1b12 was more potent in iMDDCs than in PBLs and PHA-stimulated PBMCs using both HIV-1 Bx08 and BaL. Holl *et al.* [2006b] (**neutralization, dendritic cells**)
  - IgG1b12: The ability of this Ab to inhibit viral growth was increased when macrophages and immature dendritic cells (iDCs) were used as target cells instead of PHA-stimulated PBMCs. It is suggested that inhibition of HIV replication by this Ab for macrophages and iDCs can occur by two distinct mechanisms, neutralization of infectivity involving only the Fab part of the IgG, and, an IgG-Fc $\gamma$ R-dependent interaction leading to endocytosis and degradation of HIV particles. Holl *et al.* [2006a] (**dendritic cells**)
  - b12: b12 was shown to interact with cells transiently transfected by VSV-gp120 expressing vector and stained with sera from mice immunized once intranasally with VSV vector expressing HIV-1 HXB2 gp120 indicating that VSV-HXB2 immunization produced anti-HIV-1 Abs. Jiang *et al.* [2006] (**vaccine antigen design**)
  - IgG1b12: The gp140 $\delta$ CFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. IgG1b12 was shown to bind specifically to CON-S, showing that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure, vaccine antigen design, subtype comparisons**)
  - IgG1b12: gp41 and p15E of the porcine endogenous retrovirus (PERV) share structural and functional similarities, and epitopes in the membrane proximal region of p15E are able to elicit NAbs upon immunization with soluble p15E. Rabbits immunized with a VSV recombinant expressing an HIV-1 membrane-proximal external region (MPER) fused to PERV p15E, with a fusion p15E-HIV MPER protein boost, elicited HIV specific NAbs. The IgG1b12 MAb was used as a positive control for neutralization in this study. Luo *et al.* [2006] (**vaccine antigen design**)
  - IgG1b12: The lack of glycosylation sites at residues Asn 295 and Thy 394 within C-clade gp120s generally causes the loss of 2G12 recognition. Introduction of glycans in the subtype C strain HIV-1CN54 at these positions restored 2G12 binding, and addition of just a single glycan partially restored binding (V295N + A394T  $\gg$  V295N > A395T). 2G12 epitope recovery decreased b12 binding. Chen *et al.* [2005]
  - IgG1b12: 2909 is a human anti-Env NAb that was selected by neutralization assay and binds to the quaternary structure on the intact virion. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670, 1418, nor 2G12. Gorny *et al.* [2005]

- IgG1b12: IgG1b12, like the other anti-Env broadly neutralizing MAbs 2F5 and 4E10, binds to auto-antigens and has characteristics of polyspecific autoreactive antibodies. Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. IgG1b12 reacted with ribonucleoprotein, dsDNA, centromere B, and histones, as well as nucleolar and cytoplasmic reactivity in HEp-2 cells. Haynes *et al.* [2005]
- IgG1b12: b12 and the gp41 C-terminal binding MAb SAR1 inhibit HIV-1 infected cell fusion with target cells at comparable levels. Heap *et al.* [2005a]
- IgG1b12: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Neutralization by Cameroonian sera MAbs was blocked by Clade A and B V3 loop fusion proteins, while NAb to non-V3 epitopes, 2F5, 2G12, and b12, were not blocked. Krachmarov *et al.* [2005]
- IgG1b12: Called IgG1 b12. The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using CD4BS MAbs F105 and IgG1b12, glycan-specific 2G12, and V3-specific 447-52D, and were unchanged. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Martín-García *et al.* [2005]
- IgG1b12: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potentially neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MAbs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. gp120 binding to CD4 was inhibited by b12, but not by C108g. Pinter *et al.* [2005]
- IgG1b12: Retrovirus inactivation for vaccine antigen delivery was explored through lipid modification by hydrophobic photoinduced alkylating probe 1.5 iodonaphthylazide (INA). The viral proteins were shown to be structurally intact in the treated non-infectious virus, through the preservation of antibody binding sites for polyclonal anti-gp120 serum, and for broadly neutralizing MAbs 2G12, b12 and 4E10, although the modifications of the lipid disabled viral infection. Raviv *et al.* [2005] (**vaccine antigen design**)
- IgG1b12: The antibody M2 is specific for a peptide flag inserted into the V4 loop of YU-2, a neutralization resistant variant with a short V4 loop. IgG1b12 and 2F5 could neutralize both the WT YU-2 and the modified variant. The high diversity of V4 suggests it does not play a direct role in receptor binding or viral entry, yet M2, specific for the peptide insert tag, can neutralize the modified virus, demonstrating that neutralizing activity doesn't have to block functionality of the virus. Ren *et al.* [2005] (**neutralization**)
- IgG1b12: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies in vaccinated rabbits, but GDMR elicited anti-V3 NABs. Both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4BS MAbs except Fab b12 (b6, b3, F105) did not bind to either GDMR or mCHO. CD4i MAbs (48d, 17b) did not bind even with sCD4. 2G12 had diminished binding to both. V3 MAbs (447-52D, 19b, F245-B4e8 and 39F) bound to the GDMR antigen, but either did not bind or had diminished binding to mCHO. V2 MAb 697-D did not bind to mCHO and had diminished binding to GDMR, while V2 MAb 8.22.2 bound to GDMR but not mCHO. V1/V2/V3 MAb 4KG2, C1-C4 MAb A32, C1-C5 MAb C11, and HIVIG all either did not bind or had significantly diminished binding to both antigen constructs. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- IgG1b12: The crystal structure of the Fab fragment from F105 was solved. It has an extended CDR H3 loop, with a Phe at the apex that may recognize the binding pocket of gp120 used by the Phe-42 residue of CD4. The potent NAB IgG1b12 recognizes an overlapping binding site, the main difference is that F105 extends across the interface of the inner and outer domains of gp120 while b12 does not. IgG1b12 also has undergone extensive affinity maturation (45 mutations) while F105 has not (13 mutations) – an average for gp120 MAbs is 22 mutations. Wilkinson *et al.* [2005] (**antibody sequence variable domain, structure**)
- IgG1b12: HIV-1 fusion complexes were prepared from cell lines expressing R5 HIV-1 gp120/gp41 and CD4-CCR5. Neutralizing Abs were raised against both R5 (strain BaL) and X4 (strain 213) viruses. IgG1b12 was used to detect gp120/gp41. Zipeto *et al.* [2005] (**vaccine antigen design**)
- IgG1b12: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. IgG1b12 neutralized a fraction of viruses from almost every clade, and was more potent than 2F5 and 4E10, particularly against a subset of B clade viruses. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- IgG1b12: Called b12. The peptide 12p1 (RINNIPWSEAMM) inhibits direct binding of YU2 gp120 or Env trimer to CD4, CCR5 and MAb 17b in a concentration-dependent allosteric manner. 12p1 is thought to bind to unbound gp120 near the

CD4 binding site, with a 1:1 stoichiometry. 12p1 also inhibited MAb F105 binding, presumably because F105 favors an unactivated conformation, but not 2G12 or b12. The 1:1 stoichiometry, the fact that the peptide binding site is accessible on the trimer, the non-CD4 like aspect of the binding, and an ability to inhibit viral infection in cell cultures make it a promising lead for therapeutic design. Biorn *et al.* [2004] (**antibody binding site definition and exposure**)

- IgG1b12: Env sequences were derived from 4 men at primary infection and 4 years later; the antigenicity in terms of the ability to bind to 2G12, 2F5 and IgG1b12 was determined. 2G12 bound primarily to late clones in 3 of the 4 patients, and to both early and late in the other patient. Neither 2F5 nor IgG1b12 showed a difference in binding affinity to early or late envelopes. Dacheux *et al.* [2004]
- IgG1b12: Nabs against HIV-1 M group isolates were tested for their ability to neutralize 6 randomly selected HIV-1 O group strains. IgG1b12 could neutralize some O group strains when used on its own, and quadruple combination of b12, 2F5, 2G12, and 4E10, could neutralize the six Group O viruses tested between 62-97%. Ferrantelli *et al.* [2004a]
- IgG1b12: Called b12. A set of oligomeric envelope proteins were made from six primary isolates for potential use as vaccine antigens: 92/UG/037 (clade A), HAN2/2 (clade B), 92/BR25/025 (clade C), 92/UG/021 (clade D), 93/BR/029 (clade F) and MVP5180 (clade O). This was one of a panel of MAbs used to explore folding and exposure of well characterized epitopes. The clade C isolate BR25 is apparently misfolded, as conformation-dependent antibodies did not bind to it. b12 bound to clade A, B, D and F HIV-1 primary isolates. Polyclonal sera raised in rabbits against these antigens cross-bound the other antigens, but none of the sera had neutralizing activity. Jeffs *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- IgG1b12: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of any of the five glycans, within the V3 loop (GM299 V3), C2 (GM292 C2), C3 (GM329 C3), C4 (GM438 C4), or V5 (GM454 V5) made SF162 become more sensitive to IgG1b12 neutralization. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure**)
- IgG1b12: Fab b12. A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4 viruses were more sCD4 and 2G12 neutralization resistant than either R5 or X4, but the opposite pattern was observed for b12. Addition of the late stage V1V2 altered neutralization for both MAbs, but this alteration was reversed with the loss of the V3 glycan. Nabatov *et al.* [2004] (**co-receptor**)
- IgG1b12: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it binds to the neutralizing MAb 2G12. It masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120. Pantophlet *et al.* [2004]
- IgG1b12: Called IgG-b12. V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12 which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-CD4BS MAbs were tested, including IgG1b12 which neutralizes both JRFL and SF162. The affinities for IgG1b12 and 5145A were similar for both JRFL and SF162, but 1125A bound with 2.5 fold higher affinity to SF162. 5145A and 1125H both preferentially neutralize SF162, but not JRFL, and the CD4BS is more sensitive to neutralization in the context of the SF162 V1V2 loop. This was also true for neutralization by sCD4. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- IgG1b12: Called b12. A primary isolate, CC1/85, was passaged 19 times in PBMC and gradually acquired increased sensitivity to FAb b12 and sCD4 that was attributed to changes in the V1V2 loop region, in particular the loss of a potential glycosylation site. The affinity for sCD4 was unchanged in the monomer, suggesting that the structural impact of the change was manifested at the level of the trimer. The passaged virus, CCcon19, retained an R5 phenotype and its neutralization susceptibility to other Abs was essentially the same as CC1/85. CCcon19 (IC50 0.3) was significantly more sensitive to neutralization by b12 than was CC1/85 (IC50 6.0). Pugach *et al.* [2004]
- IgG1b12: This review discusses research presented at the Ghent Workshop of prevention of breast milk transmission and immunoprophylaxis for HIV-1 in pediatrics (Seattle, Oct. 2002), and makes the case for developing passive or active immunoprophylaxis in neonates to prevent mother-to-infant transmission. Macaque studies have shown that passive transfer of NAb combinations (for example, IgG1b12, 2G12, 2F5, and 4E10) can confer partial or complete protection to infant macaques from subsequent oral SHIV challenge. Safrit *et al.* [2004]
- IgG1b12: Called IgG1 b12. This paper is a study of the 2F5 NAb complexed to peptide ELDKWAS; the peptide was found to interact with amino acids near the base of the very long (22 residue) CDR 3H region of the Ab, although a Phe at the apex of the loop was also important. The authors suggest that

- particularly long CDR H3 regions may be a common feature of HIV-1 neutralizing antibodies – there are 22 residues in 2F5's H3, 18 in IgG1b12's H3, and 22 residues in X5's H3. They express concern that because small animals like mice are unable to elicit Ab responses with such long H3s, they may be poor model systems for HIV vaccine studies. Zwick *et al.* [2004] (**antibody sequence variable domain**)
- IgG1b12: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. IgG1b12 neutralized SOS and WT proteins comparably, and neither IgG1b12 nor the Fab b12 could neutralize well post-attachment, consistent with the notion that the b12 binding site would be blocked upon cellular binding. Binley *et al.* [2003]
  - IgG1b12: Called 1b12. The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. CD4BS MAb IgG1b12 had no effect on B4e8 binding. Cavacini *et al.* [2003]
  - IgG1b12: A sCD4-17b single chain chimera was made that can bind to the CD4 binding site, then bind and block co-receptor interaction. This chimeric protein is a very potent neutralizing agent, more potent than IgG1b12, 2G12 or 2F5 against Ba-L infection of CCR5-MAGI cells. It has potential for prophylaxis or therapy. Dey *et al.* [2003]
  - IgG1b12: Four newborn macaques were challenged with pathogenic SHIV 89.6 and given post exposure prophylaxis using a combination of NAbS 2F5, 2G12, 4E10 and IgG1b12. 2/4 treated animals did not show signs of infection, and 2/4 macaques maintained normal CD4+ T cell counts and had a lower delayed peak viremia compared to the controls. Ferrantelli *et al.* [2003] (**immunoprophylaxis**)
  - IgG1b12: Called b12 – CD4BS MAbs b12 (neutralizing) and 205-42-15, 204-43-1, 205-46-9 (nonneutralizing) all cross-competed for binding to monomeric gp120, indicating the topological proximity of their epitopes, however, the nonneutralizing CD4BS MAbs did not interfere with the neutralization activity of MAb b12 – the nonneutralizing MAbs partially competed with b12 for Env binding of the surface of Env-transfected cells – this suggests Env has two categories of binding site for CD4BS MAbs, one recognized by both b12 and nonneutralizing CD4BS MAbs, the other is recognized by only b12 – Ab-gp120 interactions based on the use of monomeric gp120 or Env-transfected cells do not predict the outcome of HIV-1 neutralization assays, and they should be interpreted with caution. Herrera *et al.* [2003] (**antibody binding site definition and exposure**)
  - IgG1b12: MAbs IgG1b12, 2G12, 2F5 and 4E10 were tested for their ability to neutralize two primary HIV-1 clade A isolates (UG/92/031 and UG/92/037) and two primary HIV-1 clade D isolates (UG/92/001 and UG/92/005). 4E10 demonstrated the most potent cross-neutralization activity. Quadruple administration of MAbs IgG1b12, 2G12, 2F5, and 4E10 induced strong synergistic neutralization of 4 clade A isolates (UG/92/031, UG/92/037, RW/92/020 and RW/92/025) as well as 5 clade D isolates (UG/92/001, UG/9/005, /93/086/RUG/94/108, UG/94/114). The authors note this combination of 4 MAbs neutralizes primary HIV A, B, C, and D isolates. Kitabwalla *et al.* [2003] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - IgG1b12: This review discusses the importance and function of protective antibody responses in animal model studies in the context of effective vaccine development. SHIV models have shown protection using high levels of MAbs can prevent infection, and partial protection that can influence disease course can be obtained from modest levels of NAbS. SHIV challenges studies conducted with infusions of combinations of MAbs b12, 2G12, and 2F5 are reviewed. Mascola [2003] (**review**)
  - IgG1b12: AC10 is a subject who was given treatment early after infection, and had a viral rebound after cessation of therapy, which then declined to a low level. The polyclonal sera from AC10 could potentially neutralize the rebound virus, and NAb escape followed with a neutralizing response against the escape variant and subsequent escape from that response. Viral loads remained low in this subject despite escape. The rebound isolate that was potentially neutralized by autologous sera was not particularly neutralization sensitive, as it resisted neutralization by sCD4 and MAbs IgG1b12, 2G12 and 2F5, and was only moderately sensitive to sera from other HIV+ individuals that had high titers of NAbS to TCLA strains. Montefiori *et al.* [2003]
  - IgG1b12: Called b12 – Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 binding to those that affect binding of sCD4 and two non-neutralizing anti-CD4BS Abs b3 and b6 – while the epitope maps overlapped, there were some differences observed – binding of CD4 was never enhanced, indicating it had evolved to be optimal – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished – 2G12 binding was largely unperturbed, indicating these proteins were not grossly misfolded – for twelve mutants, b12 neutralization sensitivity and affinity correlated, but for five mutants neutralization efficiency was maintained or increased despite a decrease in affinity suggesting that the substitutions that influence b12 binding to the monomer are different than those that impact neutralization sensitivity to the trimer. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
  - IgG1b12: This paper describes an attempt to engineer a gp120 molecule that would focus the immune response onto the IgG1b12 epitope. Four Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with seven N-linked glycosylation site sequons and this combination minimized the binding of non-neutralizing MAbs. b12 affinity was lowered, and binding of non-neutralizing MAbs was knocked out. C1 and C5 regions were then removed to eliminate the epitopes for MAbs against these regions, but these also diminished IgG1b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
  - IgG1b12: Virion capture assays are not a good predictor of

neutralization, and the presentation of epitopes using this assay seems to be different from that of functional Envelope spikes on primary isolates – F105 and b6 could efficiently block the b12-mediated capture of infectious virions in a virus capture, but did not inhibit b12 neutralization – b12 was potent at neutralizing the three primary virions JR-CSF, ADA, and 89.6, but anti-V3 Abs 447-52D and 19b, which did not neutralize JR-CSF and ADA captured amounts of p24 equal to or higher than the amounts captured by the neutralizing Ab b12. Poignard *et al.* [2003] (**neutralization**)

- IgG1b12: This paper shows that binding of CD4BS MAbs to Env blocks the conformational shift that allows co-receptor CCR5 binding and CD4-independent mediated cell fusion. CD4BS MAbs F105, 15e, and IgG1b12 as well as their Fab fragments inhibited CD4-independent binding of the V1/V2 loop-deleted gp120 glycoproteins of R5 HIV-1 isolates ADA, YU2 and JR-FL and to CCR5 in a concentration dependent manner. CD4BS MAbs IgG1b12, F91 and F105 and their Fab counterparts (except for C11, used as a negative control) inhibited CD4-independent JR-FL and YU-2 gp120-CCR5 binding to CCR5-expressing Cf2Th cells and syncytium formation. Raja *et al.* [2003] (**antibody binding site definition and exposure**)
- IgG1b12: Called b12. The NAb b12 was administered locally to the vagina in macaques and could protect against subsequent vaginal infection with SHIV-162P4. This NAb model of a topical microbicide was dose dependence, and was effective for up to 2 hours after administration. Veazey *et al.* [2003] (**immunoprophylaxis**)
- IgG1b12: Called b12. Review of current neutralizing antibody-based HIV vaccine candidates and strategies of vaccine design. Strategies for targeting of the epitopes for NAb 2F5, 2G12, 4E10, b12, and Z13 are described. Wang [2003] (**review**)
- IgG1b12: Called b12. The Fab m18 was selected from a human phage display library by a new method called sequential antigen panning (SAP), using a series of antigens to screen the library to pick broadly cross-reactive isolates. The ability to block cell mediated fusion by m17 was compared to Fabs X5 and b12 for a clade A, CRF01 EA, G, and 6 clade B isolates, and the inhibitory activity of m18 was slightly lower but comparable to neutralizing Fabs b12 and X5. Zhang *et al.* [2003]
- IgG1b12: The HIV-1 primary isolate DH012 has preserved the epitopes for the MAbs IgG1b12, 2G12, 17b, however natural DH012 infection in chimpanzees and DH012 gp120 vaccination in guinea pigs does not give rise to Abs against these epitopes. Zhu *et al.* [2003] (**vaccine antigen design**)
- IgG1b12: 4KG5, a single-chain Fv (scFv), reacts with a conformational epitope that is formed by the V1, V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Denaturation of gp120 abolished binding of 4KG5 and Fab b12. Additionally, binding of 4KG5 was abrogated when any of the V1, V2 or V3 loops were deleted. Of a panel of Abs tested, only NAb b12 enhanced 4KG5 binding to gp120 JR-FL. MAbs to the following regions diminished or abrogated binding: V2 loop MAbs (G3-4, G3-136), V3 loop MAbs (19b, 447-52D, hNM01, AH48, loop2, F425 B4e8, 694-88D), V3-C4 (G3-299, G3-42, G3-519, G3-537), CD4BS (b6, b3, F91, F105, 15e, L33, 1008-D, 654-30D, 559-64D, 1027-30D, Ia3, Ia7, FG39, Fbb14). MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1, V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. 4KG5 did not enhance IgG1b12 neutralization. Zwick *et al.* [2003] (**antibody interactions**)
- IgG1b12: IgG1b12 neutralized many South African (5/8) and Malawian (4/8) clade C primary HIV-1 isolates, being more effective than 2F5 which neutralized only two Malawian and no South African isolates. 2G12 did not neutralize any of the 16 isolates. Bures *et al.* [2002] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- IgG1b12: This study examined Ab interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-gp41 MAb F240 enhanced the binding of CD4BS MAbs IgG1b12 and F105 to both R5X4 and R5 isolates, but had no effect on neutralization. Anti-V3 MAb B4a1 increased CD4BS MAbs IgG1b12 and F105 to R5X4 virions, but only IgG1b12 binding was increased by B4a1 to the R5 isolate, and neutralization was not impacted. Cavacini *et al.* [2002] (**antibody interactions**)
- IgG1b12: A modified gp140 (gp140ΔCFI), with C-term mutations intended to mimic a fusion intermediate and stabilize trimer formation, retained antigenic conformational determinants as defined by binding to CD4 and to MAbs 2F5, 2G12, F105, and b12, and enhanced humoral immunity without diminishing the CTL response in mice injected with a DNA vaccine. Chakrabarti *et al.* [2002]
- IgG1b12: Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**antibody binding site definition and exposure**)
- IgG1b12: Review of NAb that notes IgG1b12 is a recombinant IgG1 from a phage displayed Fab generated against gp120 from a B clade infected individual, that it binds the CD4BS, that alone or in combination with other MAbs it can protect some macaques against SHIV infection, and that it has strong ADCC activity. Ferrantelli & Ruprecht [2002] (**review**)
- IgG1b12: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b. Golding *et al.* [2002b]



- IgG1b12: HIV-1 gp160 $\Delta$ CT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines—2F5 bound to gp160 $\Delta$ CT with a reconstituted membrane ten-fold better than the same protein on beads—anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160 $\Delta$ CT PLs indistinguishably from gp160 $\Delta$ CT expressed on the cell surface—non-neutralizing MAbs C11 and A32 bound with lower affinity than NAb IgG1b12—the MAb 17b was sCD4 inducible on gp160 $\Delta$ CT PL. Grundner *et al.* [2002]
- IgG1b12: A broad review of NABs that mentions IgG1b12 as an example of a NAB that does not alter the conformation of gp120, but interferes with CD4 binding. Klasse & Sattentau [2002] (review)
- IgG1b12: Called b12. Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. Enthalpy and entropy changes were divergent, but compensated. CD4 and MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy of binding to the gp120 monomer (mean: 26.1 kcal/mol, range 18.6-31.5), but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding and ordering of amino acids upon binding. NAb 2G12 had an entropy value of -1.6. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding that is not faced by other anti-gp120 antibodies. Kwong *et al.* [2002] (structure)
- IgG1b12: Recombinant adeno-associated virus was used to deliver the IgG1b12 gene into mice by injection. IgG1b12 was expressed in these mice for over 6 months after the primary injection. This strategy allows for predetermined Ab specificity, and could ultimately be used with synergistic Ab combinations. Lewis *et al.* [2002]
- IgG1b12: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Ling *et al.* [2002]
- IgG1b12: Review of NABs that discusses mechanisms of neutralization, passive transfer of NABs and protection in animal studies, and vaccine strategies. Liu *et al.* [2002] (review)
- IgG1b12: Deglycosylation of gp120 does not significantly affect IG1b12 binding, in contrast to MAB 2G12. Sanders *et al.* [2002] (antibody binding site definition and exposure)
- IgG1b12: The crystal structure of IgG1b12 is resolved and is the first structure of an intact human Ab with an ordered, full length hinge – the structure is extremely asymmetric and flexible with an antigen-binding site that has an unusually long CDR H3 region with a ten residue insertion that projects above the rest of the antigen-binding site – this loop may be required for recognition of the recessed CD4 binding site of gp120. Saphire *et al.* [2002] (antibody binding site definition and exposure, antibody sequence variable domain, structure)
- IgG1b12: Alanine scanning mutagenesis used in conjunction with competition and replacement studies of N-linked carbohydrates and sugars suggest that the 2G12 epitope is formed from mannose residues contributed by the glycans attached to N295 and N332, with the other N-linked carbohydrates in positions N339, N386, and N392 playing a role in maintaining conformation relevant to 2G12 binding – N295A and N332A mutants showed essentially unchanged anti-CD4BS NAb b12 binding affinities, while N339A, N386A and N392A mutants displayed significantly lowered b12 affinity, presumably due to conformational changes. Scanlan *et al.* [2002] (antibody binding site definition and exposure)
- IgG1b12: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NABs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140 – SOS gp140-2F5-IgG1b12 formed multiple ring structures composed of two SOS gp140 proteins bridged by two Ab molecules, while 2F5 and 2G12 formed extended chains rather than closed rings. Schulke *et al.* [2002] (vaccine antigen design)
- IgG1b12: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – Abs directed against the CD4 binding site (Ig-GCD4 and IgG1b12) reacted slightly more strongly with the gp120 monomer than with the oligomer, as did sCD4. Srivastava *et al.* [2002] (antibody binding site definition and exposure, vaccine antigen design)
- IgG1b12: Called ARP3065: Herpesvirus saimiri-immortalized CD4+ T lymphocytes (HVS T cells) were used to isolate virus and perform HIV-1 neutralization assays, and compared with a standard PBMC protocol – neutralization sensitivities to a panel of MAbs and to homologous or heterologous plasma/sera were similar for HVS T cells (CN-2 cells) and PBMCs. Vella *et al.* [2002] (neutralization)
- IgG1b12: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (antibody binding site definition and exposure, neutralization)

- IgG1b12: Passive immunization of neonate macaques with a combination of F105+2G12+2F5 conferred complete protection against oral challenge with SHIV-vpu+ or – the combination b12+2G12+2F5 conferred partial protection against SHIV89.6 – such combinations may be useful for prophylaxis at birth and against milk born transmission – the synergistic combination of IgG1b12, 2G12, 2F5, and 4E10 neutralized a collection of HIV clade C primary isolates. Xu *et al.* [2002]
- IgG1b12: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibrin—stabilized oligomer gp140Δ683(-FT) showed strong preferential recognition by NAb IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAb F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002] (**vaccine antigen design**)
- IgG1b12: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAb directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**antibody binding site definition and exposure**)
- IgG1b12: Called IgG1 b12. IgG1b12 induces strong ADCC and CDC cytotoxicity of HIV-1 infected cells. A panel of mutants in the Fc region of IgG1b12 was generated. K322A reduced ADCC binding of FcγR and abolished complement-dependent cytotoxicity (CDC) and C1q binding. L234A plus L235 in the lower hinge region of the IgG1 heavy chain abolished both FcγR and C1q binding and ADCC and CDC. These mutants did not impact IgG1b12's ability to neutralize virus. Hezareh *et al.* [2001]
- IgG1b12: A combination of MAbs IgG1b12, 2F5, and 2G12 was given postnatally to four neonates macaques that were then challenged with highly pathogenic SHIV89.6P – one of the four infants remained uninfected after oral challenge, two infants had no or a delayed CD4(+) T-cell decline – the most potent combination included IgG1b12, which alone does not alone neutralize SHIV89.6P. Hofmann-Lehmann *et al.* [2001] (**antibody interactions, immunoprophylaxis**)
- IgG1b12: Mutations in two glycosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYR-LINCNTS) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, except the mutation 197 S/R which resulted in a carbohydrate addition to 195 N that disrupts the IgG1b12 binding site. Kolchinsky *et al.* [2001] (**antibody binding site definition and exposure**)
- IgG1b12: Intravenous passive transfer of MAb b12 provides dose-dependent protection from infection to macaques vaginally challenged with the R5 virus SHIV(162P4) – the primary isolate HIV-1SF162 is neutralized 90% (IC90) by b12 at 2 μg/ml, and SHIV162P4, derived from HIV-1SF162, was neutralized by 90% at 2 μg/ml in PHA-activated PBMC from rhesus macaques – the 90% neutralization titers achieved in three groups of animals that were given 25-, 5-, and 1-mg/kg doses were approximately 1:400, 1:80, and 1:16, respectively – the half-life of IgG1 b12 in plasma was about 1 week, but while the peak b12 plasma concentration was immediately after the infusion, the peak vaginal fluid concentration was 7-14 days later. Parren *et al.* [2001] (**immunoprophylaxis, kinetics**)
- IgG1b12: Structural aspects of the interaction of neutralizing Abs with HIV-1 Env are reviewed – Env essentially has three faces, one is largely inaccessible on the native trimer, and two that exposed but have low immunogenicity on primary viruses – neutralization is suggested to occur by inhibition of the interaction between gp120 and the target cell membrane receptors as a result of steric hindrance and it is noted that the attachment of approximately 70 IgG molecules per virion is required for neutralization, which is equivalent to about one IgG molecule per spike – the 2G12, 17b and b12 epitopes are discussed in detail – the structure of CD4-bound gp120 reveals features that HIV has evolved to escape anti-CD4BS Abs like IgG1b12 despite profound functional constraints – CD4BS Abs must first access the CD4 binding site, deeply recessed within the gp120 core, and the Fab of an Ab molecule is "wider" than CD4, and in addition the binding site is flanked by variable and glycosylated regions. Poignard *et al.* [2001] (**review, structure**)
- IgG1b12: This paper describes the technical aspects of the crystallization of b12 at a resolution of 2.7 angstroms with all 12 Ig domains resolved. Saphire *et al.* [2001a] (**structure**)
- IgG1b12: This paper describes the biological implications of the crystal structure of b12 – a remarkable feature of this antibody is a long protruding finger-like CDR H3 that can dock in the recessed CD4-binding site – a contact residues in gp120 are modeled, with numbering based on the variable loop-deleted crystal structure of gp120. Saphire *et al.* [2001b] (**structure**)
- IgG1b12: SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkey's yielded highly pathogenic SHIV KU-1 – HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160 – substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1 – 17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001]
- IgG1b12: A luciferase-reporter gene-expressing T-cell line was developed to facilitate neutralization and drug-sensitivity assays – luciferase and p24 antigen neutralization titer end points were found comparable using NAb from sera from HIV+ donors, and MAbs 2F5, 2G12 and IgG1b12. Spelnhauer *et al.* [2001] (**assay development**)
- IgG1b12: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 μg/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutral-

- izing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 M Abs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions, co-receptor**)
- IgG1b12: Twenty HIV clade C isolates from five different countries were susceptible to neutralization by anti-clade B MAbs in a synergistic quadruple combination of mAbs IgG1b12, 2G12, 2F5, and 4E10. Xu *et al.* [2001] (**subtype comparisons**)
  - IgG1b12: Primary isolates YU2 and ADA are more resistant to IgG1b12 neutralization than HXBc2: 90% Neutralization of HXBc2 is observed with 1.25 ug of IgG1b12, while ADA and YU2 require 2.5 and 5 ug respectively to achieve 50% neutralization, and 90% neutralization could not be achieved with 10 or 20 ug of IgG1b12, respectively. Yang *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
  - IgG1b12: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding. York *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
  - IgG1b12: Neutralizing synergy between MAbs 1b12, 2G12 and 2F5 was studied using surface plasmon resonance to determine the binding kinetics for these three MAbs with respect to monomeric and oligomeric env protein gp160 IIIB – the 2G12 epitope is highly accessible on both monomeric and oligomeric Envs, 1b12 is highly accessible on monomers but not oligomers, and 2F5 on neither form – binding of 2G12 exposes the 2F5 epitope on gp160 oligomers. Zeder-Lutz *et al.* [2001] (**antibody interactions**)
  - IgG1b12: b12 recognizes a conformational epitope that overlaps with the CD4 binding site – a phage displayed peptide library was used to identify a peptide which bound b12, called B2.1, which competes with b12 in competition assays – B2.1 has significant homology to the D loop of gp120: upper case letters indicate residues B2.1 shares with gp120, heRsymFS-DlenrcI – one of the goals of defining peptide mimics to the b12 epitope is to develop an immunogen that can stimulate b12-like antibodies, but B2.1 cross-linked to phage and ovalbumin bound IgG1b12 did not elicit cross-reactive gp120 Abs in mice or rabbits. Zwick *et al.* [2001a] (**antibody binding site definition and exposure, mimotopes**)
  - IgG1b12: This paper primarily concerns 4E10 and Z13, MAbs that both bind proximally to the 2F5 binding site to a conserved epitope, and that neutralize some primary isolates from clades B, C, and E – broadly neutralizing MAbs 2F5, IgG1b12, and 4E10 and Z13 fail to neutralize different subsets of viruses. Zwick *et al.* [2001b] (**subtype comparisons**)
  - IgG1b12: Neutralization synergy between anti-HIV NAbs b12, 2G12, 2F5, and 4E10 was studied – a classic fixed-ratio method was used, as well as a method where one Ab was fixed at a low neutralization titer and the other was varied – using primary isolates, a two-four fold enhancement of neutralization was observed with MAb pairs, and a ten-fold enhancement with a quadruple Ab combination – no synergy was observed with any MAb pair in the neutralization of TCLA strain HXB2 – whole IgG1b12 and b12 Fab fragments behaved similarly in the neutralization assays – there was no evidence for cooperativity of binding between b12 and 2G12 to envelope spikes expressed on the cell surface of TCLA or primary isolates. Zwick *et al.* [2001c] (**antibody interactions**)
  - IgG1b12: To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**vaccine antigen design**)
  - IgG1b12: SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not enhance neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows increased infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000] (**escape**)
  - IgG1b12: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 CD4BS MAbs – CD4BS MAbs bound consistently to most isolates of clade D, but poorly to isolates of other clades with the exception of broadly reactive MAb IgG1b12, binding to 22 of 26 isolates tested – 8 MAbs were tested for neutralization and MAb IgG1b12 was most potent, with 90% neutralization of 3/5 isolates tested. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - IgG1b12: Fab b12 was used – six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
  - IgG1b12: rgp120 derived from a R5X4 subtype B virus was used to vaccinate healthy volunteers and the resulting sera were compared with sera from HIV-1 positive subjects and neutralizing MAbs – TCLA strains showed enhanced IgG1b12 neutralization sensitivity relative to PBMC-adapted lines – IgG1b12 was able to bind, with low affinity, to the rgp120 monomer HIV-1 W61D. Beddows *et al.* [1999] (**co-receptor**)
  - IgG1b12: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 re-

- gion MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**vaccine antigen design**)
- IgG1b12: Neutralization assays with rsCD4, MAbs, and serum samples from SHIV-infected macaques and HIV-1 infected individuals were used to characterize the antigenic properties of the env glycoprotein of six primary isolate-like or TCLA SHIV variants. IgG1b12 neutralized SHIV strains HXBc2, KU2, 89.6, but not 89.6P and KB9. 89.6 is a dual tropic primary isolate that is not pathogenic in macaques, 89.6P is a highly pathogenic form of 89.6 obtained after passage in macaques, and KB9 is a molecular clone of 89.6P. Neutralization resistance was cell line independent. Crawford *et al.* [1999] (**variant cross-recognition or cross-neutralization**)
  - IgG1b12: The presence of leukocyte function-associated molecule 1 (LFA-1) promotes virus infectivity and hinders neutralization, and anti-LFA-1 MAbs can enhance the neutralizing effect of anti-HIV V3 MAb 447-52D and anti-HIV CD4BS MAb IgG1b12 – non-neutralizing anti-HIV CD4BS MAb 654-D did not become neutralizing in the presence of anti-LFA-1 MAbs. Hioe *et al.* [1999] (**antibody interactions**)
  - IgG1b12: does not inhibit attachment of virus to cells and was used as a control of a study of neutralization by a MAb F58 based micro antibody. Jackson *et al.* [1999]
  - IgG1b12: A meeting summary presented results regarding neutralization – D. Burton and J. Mascola presented results concerning passive immunization and protection of hu-PBL-SCID mice and macaques, respectively, and both found combinations of MAbs that were able to achieve 99% neutralization *in vitro* corresponded to efficacy *in vivo*. Montefiori & Evans [1999] (**review**)
  - IgG1b12: Hu-PBL-SCID mice were infected with HIV-1s JRCSF and SF162 to study the effect of NAb on an established infection – at day 6 post infection, mice were given 50 mg/kg of b12, an amount that would have been protective if given up to 8 hours post-infection, and 100-fold higher than the amount required for 90% neutralization *in vitro* – no significant differences in the initial rate of decrease in viral load or the plateau levels of viral RNA between the b12 treated and control mice were seen – in most of the Ab treated mice escape mutants were observed with varying patterns of mutations – a combination of b12, 2G12 and 2F5 protected 1/3 mice, and an isolate from one of the other two was resistant to neutralization by all three MAbs. Poignard *et al.* [1999] (**escape, immunotherapy**)
  - IgG1b12: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – CD4BS MAbs 15e, F91 and IgG1b12 bound better to the deleted protein than to wild type. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
  - IgG1b12: Immunoprecipitation of gp120 and gp160 expressed from a rec Semliki Forest virus by F105 and IgG1b12 indicated that the SFV expressed HIV-1 Env was folded appropriately – and SVF-HIV-1 Env vaccine gave the strongest anti-HIV-1 Env response in mice, when compared to an HIV-1 Env DNA vaccine and a rgp160 protein. Brand *et al.* [1998] (**vaccine antigen design**)
  - IgG1b12: Ab from gp120 vaccinated individuals prior to infection, who subsequently became HIV infected, could not achieve 90% neutralization of the primary virus by which the individuals were ultimately infected – these viruses were not particularly refractive to neutralization, as determined by their susceptibility to neutralization by MAbs 2G12, IgG1b12, 2F5 and 447-52D. Connor *et al.* [1998] (**variant cross-recognition or cross-neutralization**)
  - IgG1b12: Binds JRSF oligomer with high affinity, as do 205-46-9 and 2G6, but IgG1b12 is neutralizing, the other two are not – conclusions of this paper contrast with Parren98 – authors propose a model where 205-46-9 and 2G6 may inhibit CD4 binding, but cause a conformational shift which enhances CCR5 binding and thus counteracts the neutralizing effect – rank order of CD4BS antibodies oligomer binding is IgG1b12 = 2G6 = 205-46-9 > 205-43-1 = 205-42-15 > 15e = 21h = F91, and the only thing notably distinguishing about neutralizing IgG1b12 is that it depends on residues in V2. Fouts *et al.* [1998] (**antibody binding site definition and exposure**)
  - IgG1b12: Infection of dendritic cells cultured from CD14+ blood cells or from cadaveric human skin was blocked by neutralizing MAbs IgG1b12, or 2F5 and 2G12 delivered together, but not by control non-neutralizing anti-gp120 MAb 4.8D, indicating that NAb could interrupt early mucosal transmission events. Frankel *et al.* [1998] (**antibody interactions, mucosal immunity**)
  - IgG1b12: anti-C1 region MAb 87-135/9 blocks gp120 interaction with CD4+ cells – blocking activity is additive when combined with antibodies which bind in the C4 region of gp120 (F105, 388/389, and b12). Kropelin *et al.* [1998] (**antibody interactions**)
  - IgG1b12: Enhances binding of Hx10 to CD4 positive or negative HeLa cells, inhibits binding to CD4+ T-cell line A3.01 – neutralizes HeLa and A3.01 cell Hx10 infection. Mondor *et al.* [1998]
  - IgG1b12: IgG1b12, Fab b12 and 3B3 derived from b12 were all included in this study – the rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope – binding affinity of divalent IgG1b12 is 17-fold greater than monovalent Fab b12. Parren *et al.* [1998a] (**binding affinity**)
  - IgG1b12: MAbs 2G12, 2F5 and b12 are broadly neutralizing, as are some human polyconal sera, but this paper describes a set of primary isolates that are resistant to all three MAbs

- and 2 broadly neutralizing sera – results indicate that resistance levels of pediatric isolates might be higher than adult isolates – resistance in general did not seem to be conferred by a loss of binding affinity for gp120 or gp41, rather by a more global perturbation of oligomeric Envelope. Parren *et al.* [1998b] (**variant cross-recognition or cross-neutralization, responses in children**)
- IgG1b12: MAbs 654-D100 and IgG1b12 neutralized viruses HIV-BRU and a mutated virus that lacks the V3 loop glycan equally effectively – in contrast, sera from guinea pigs immunized with BRU gp120 neutralize viruses more effectively that lack the V3 glycan. Schonning *et al.* [1998] (**antibody binding site definition and exposure**)
  - IgG1b12: Deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V2, but not V1, diminished neutralization by CD4BS MAb IgG1b12, in contrast to 654.30D and IgGCD4. Stamatatos & Cheng-Mayer [1998] (**vaccine antigen design**)
  - IgG1b12: Fab b12 – the HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – Fab fragment b12 also enhances YU2 entry, ruling out Fc interactions or Env cross-linking as a mechanism, while neutralizing HXBc2. Sullivan *et al.* [1998a]
  - IgG1b12: Induces Complement-mediated lysis in MN but not primary isolates – primary isolates are refractive to CML. Takefman *et al.* [1998] (**complement**)
  - IgG1b12: MAb was slightly more efficient at neutralization than Fab – inhibits viral binding to cells and viral entry – doesn't affect CD4-independent binding to T-cells. Valenzuela *et al.* [1998]
  - IgG1b12: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAb binding – probable mechanism of neutralization by CD4BS Ab is direct interference with CD4 binding – IgG1b12 is an unusual CD4BS antibody because it is particularly potent as a neutralizing antibody and it is susceptible to changes in the V1-V2 stem loop structure, and so it may disrupt an interaction between CD4 and conserved amino acids on the V1-V2 stem. Wyatt *et al.* [1998] (**structure**)
  - IgG1b12: Abs that recognize discontinuous epitopes can identify mimotopes from a phage peptide display library – IgG1b12 blocks CD4 binding and is the most potent neutralizing Ab – many 15 and 21-mer phage inserts were recognized, but it was not possible to derive a consensus – common features were a W and at least one acidic residue, and one sequence was found multiple times: NWPRWEEFVD-KHSS, and this peptide could compete with gp120 – two short stretches found in the phage peptides might mimic gp120 components of the epitope: positions 382-384, FFY(I), and 423-426 I(FV)I(V)NM. Boots *et al.* [1997] (**mimotopes**)
  - IgG1b12: This is a review that includes a description of IgG1b12, noting approximately equivalent affinities for sgp120 and unprocessed gp160, and somewhat enhanced affinity for the native oligomer on TCLA viruses – primary viruses have reduced affinity, but still in the useful range for neutralization – there can be complete protection in hu-PBL-SCID mice with Ab even when administered several hours after viral challenge – competes with sCD4, but unlike other CD4BS antibodies, it is sensitive to mutations in V2. Burton & Montefiori [1997] (**review**)
  - IgG1b12: In a multilab evaluation of monoclonal antibodies, only IgG1b12, 2G12, and 2F5 could neutralize at least half of the 9 primary test isolates at a concentration of < 25 mug per ml for 90% viral inhibition – IgG1b12 failed to neutralize only 1/9 primary isolates, although there was some variation between test sites. D'Souza *et al.* [1997] (**variant cross-recognition or cross-neutralization, assay standardization/improvement**)
  - IgG1b12: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – IgG1b12 bound monomer, oligomer, and neutralized JRFL. Fouts *et al.* [1997] (**antibody binding site definition and exposure**)
  - IgG1b12: b12 was used in its IgG1 form – of 14 human MAbs, the most potent neutralizer of SHIV-vpu+, which expressed HIV-1 IIIB env – all Ab combinations tested showed synergistic neutralization – b12 has a synergistic response with MAbs 694/98-D (anti-V3), 2F5, and 2G12. Li *et al.* [1997] (**antibody interactions**)
  - IgG1b12: JRCSF was cultured in the presence of IgG1b12 until a 100-fold resistance to neutralization was selected – resistance was due to three changes: V2 substitution D182N and C3 substitution P365L conferred resistance, and V2 D164N was also required for a viable virus – IgG1b12 resistant virus remained sensitive to MAbs 2G12 and 2F5. Mo *et al.* [1997] (**escape**)
  - IgG1b12: Review: MAbs 2F5, 2G12 and IgG1b12 have potential for use in combination with CD4-IgG2 as an immunotherapeutic or immunoprophylactic – homologous MAbs to these are rare in humans and vaccine strategies should consider including constructs that may enhance exposure of these MAbs' epitopes. Moore & Trkola [1997] (**review**)
  - IgG1b12: Complete protection against HIV-1 infection was achieved in hu-PBL-SCID mice by passive immunization with physiologically relevant doses – pharmacokinetics showed serum half-life of 30.2 +/- 1.3 hours for Fab b12 and 7.4 +/- 0.7 days for IgG1 b12 in mice, but IgG1 half-lives in human are generally between 21-23 days. Parren *et al.* [1995]; Parren & Burton [1997] (**immunoprophylaxis**)
  - IgG1b12: In this review, the technique and potential application of Fab expression and selection in phage display libraries, and subsequent production of IgG molecules is discussed – b12 is exceptionally potent at neutralization and can successfully neutralize most B clade primary isolates, and many isolates from other subtypes as well – 3B3 was derived from b12 by selection for higher affinity using the CDR walking strategy – 3B3 has 8-fold enhancement of binding, a linear correlation was found between neutralization and affinity, and 3B3

- can neutralize strains b12 cannot. Parren & Burton [1997] (**binding affinity, review**)
- IgG1b12: Fab b12 is unusual in that it binds to gp140 and monomeric gp120 with similar affinities, and with a higher affinity to the native oligomer—authors propose this antibody may be exceptional because it binds the virus rather than viral debris—IgG1b12 can protect against infection prior to or shortly after challenge of hu-PBL-SCID mice with TCLA strains and primary strains, but the serum concentrations required *in vivo* were higher than for *in vitro* neutralization. Parren *et al.* [1997b,a] (**antibody binding site definition and exposure, immunoprophylaxis**)
  - IgG1b12: Inhibited some SI- and NSI-env chimeric viruses but enhanced one NSI-env chimeric virus 3 fold. Schutten *et al.* [1997] (**enhancing activity, variant cross-recognition or cross-neutralization**)
  - IgG1b12: Viral binding inhibition by IgG1b12 strongly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5). Ugolini *et al.* [1997]
  - IgG1b12: Major deletions in C1 and C5 and deletions of the V1V2 and V3 loops do not diminish binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
  - IgG1b12: Saturation mutagenesis of the complementarity-determining region and optimization strategies were used to create very high affinity versions of this Fab – increased affinity was dominated by a slowing of the off rate. Yang *et al.* [1997c] (**binding affinity**)
  - IgG1b12: 35 primary isolates were tested and all were neutralized by IgG1b12 (including 4, UG270, RW92/026, ZB20, and 301727 which been had reported as not neutralized by IgG1b12 Trkola *et al.* [1995]) – IgG1b12 could neutralize even when added after the virus to the culture – selection for 400-fold increased affinity did not enhance neutralization by antibody – IgG1b12 was more potent with greater breadth than MAb 2F5 Kessler II *et al.* [1997]. Kessler II *et al.* [1997]; Trkola *et al.* [1995] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - IgG1b12: Potent neutralizing *ex vivo* of virus taken directly from plasma of HIV-1 infected individuals – little correlation between neutralization sensitivity of passaged virus and plasma derived virus – more effective than MAb 19b. Gauduin *et al.* [1996] (**antibody interactions**)
  - IgG1b12: Review: Unique among anti-CD4BS MAbs in terms of being potent against both lab adapted virus and primary isolates – one of three MAbs (IgG1b12, 2G12, and 2F5) generally accepted as having significant potency against primary isolates. Poignard *et al.* [1996b] (**review**)
  - IgG1b12: Anti-CD4BS MAbs 15e, 21h, and IgG1b12 did not cause gp120 dissociation from virus, or exposure of the gp41 epitope of MAb 50-69, in contrast to CD4i MAb 48d and anti-V3 neutralizing MAbs. Poignard *et al.* [1996a] (**antibody interactions**)
  - IgG1b12: Review: Only four epitopes have been described which can stimulate a useful neutralizing response to a broad spectrum of primary isolates, represented by the binding sites of MAbs: 447-52-D, 2G12, Fab b12, and 2F5. Sattentau [1996] (**review**)
  - IgG1b12: Neutralizes JR-FL – inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**antibody binding site definition and exposure**)
  - IgG1b12: Because Fab b12 shows reduction in binding when the V2 loop is deleted and when aa 183/184 PI/SG substitutions are made competition studies were done with Fab L78 and anti-V2 MAbs SC258 and 684-238 and they do not compete with IgG1b12. Ditzel *et al.* [1995] (**antibody interactions**)
  - IgG1b12: Called BM12 – broad cross-clade neutralization of primary isolates – additive neutralization in combination with MAb 2F5. Kessler *et al.* [1995] (**antibody interactions**)
  - IgG1b12: Anti-CD4 binding site MAb – very potent neutralization of a number of primary isolates. Moore *et al.* [1995a]
  - IgG1b12: Review: unusual properties for anti-CD4 BS MAb: sensitive to V2 substitutions, preferential recognition of the oligomer on the cell surface. Moore & Ho [1995] (**review**)
  - IgG1b12: Formalin inactivation of virus at 0.1% formalin for 10 hours at 4 degrees was optimal for inactivation of virus while maintaining epitope integrity. Sattentau *et al.* [1995]
  - IgG1b12: Fab b12 showed potent neutralization of T-cell-line-adapted strains, but much reduced neutralization of 3 primary isolates – 2 of the 3 primary isolates also had reduced binding affinity, but the third was as efficiently immunoprecipitated as HXBc2. Sullivan *et al.* [1995] (**variant cross-recognition or cross-neutralization**)
  - IgG1b12: Could potentially neutralize primary isolates from within clade B, but showed a slight reduction in efficacy outside of clade B. Trkola *et al.* [1995] (**subtype comparisons**)
  - IgG1b12: Very potent neutralization, of primary and lab strains, at concentrations that could be achieved by passive immunization – reduced binding with A,C, and D clade viruses relative to B clade, poor reactivity with E clade – isolates that were refractive to neutralization by sera from HIV-1 + donors could be neutralized by IgG1 b12. Burton *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
  - IgG1b12: Cross-reactive with some gp120s, (but not all), from clades A-D – not reactive with gp120 from clades E or F. Moore *et al.* [1994b] (**variant cross-recognition or cross-neutralization**)
  - IgG1b12: Anti-CD4 binding site Fab, potent neutralizing activity, greater affinity for a subpopulation of gp120 molecules suggested to be in a mature conformation – mutations in gp120 that abrogate binding: 368 D/R or D/T, 370 E/R, and 477 D/V, of clone HXBc2 of LAI – sensitive to V1 and V2 substitutions. Roben *et al.* [1994] (**antibody binding site definition and exposure**)
  - IgG1b12: The original Fab fragment was derived from a combinatorial phage library from bone marrow of an HIV-1 positive individual who had been asymptomatic for six years. Burton *et al.* [1991] (**antibody generation**)

No. 1191

MAb ID IgGCD4 (IgG-CD4)

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing

Immunogen

Species (Isotype) human (IgG)

**Ab Type** gp120 CD4BS

**References** Srivastava *et al.* 2002; Ly & Stamatatos 2000; Stamatatos & Cheng-Mayer 1998; Capon *et al.* 1989

- IgGCD4: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MABs – Abs directed against the CD4 binding site (IgGCD4 and IgG1b12) reacted slightly more strongly with the gp120 monomer than with the oligomer, as did sCD4. Srivastava *et al.* [2002]
- IgGCD4: SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MABs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MABs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MABs (G3.4 and G3.136) or CD4i MABs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000]
- IgGCD4: Deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V2 but not V1 slightly enhanced neutralization by CD4BS MAB IgGCD4. Stamatatos & Cheng-Mayer [1998]
- IgGCD4: An antibody-like immunoadhesins molecule was constructed incorporating the gp120-binding domain of CD4. Capon *et al.* [1989]

**No.** 1192

**MAB ID** L28

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995

**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, review

- L28: This review summarizes MABs directed to HIV-1 Env. There are 51 CD4BS MABs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- L28: Substitutions at 257 T/R, 368 D/R, 370 E/R and 370 E/Q, 475 M/S 102 E/L and 463 N/D reduce binding – binding was enhanced by removal of the V3 loop and by substitutions 45 W/S, 298 R/G, 381 E/P, 382 F/L, 420 I/R, 435 Y/H or Y/R – binding is sensitive to deglycosylation – heavy and light chain variable region sequence is available. Ditzel *et al.*

[1995] (**antibody binding site definition and exposure, antibody sequence variable domain**)

**No.** 1193

**MAB ID** L33

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Zwick *et al.* 2003; Ditzel *et al.* 1995

**Keywords** antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, review

- L33: This review summarizes MABs directed to HIV-1 Env. There are 51 CD4BS MABs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- L33: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MABs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MABs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MABs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MABs used. Zwick *et al.* [2003] (**antibody interactions**)
- L33: binding is sensitive to deglycosylation – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure, antibody sequence variable domain**)

**No.** 1194

**MAB ID** L41

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995

**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, review

- L41: This review summarizes MABs directed to HIV-1 Env. There are 51 CD4BS MABs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- L41: Substitutions at 133 D/R, 256 S/Y, 257 T/R, 368 D/R or D/T, 370 E/Q or E/R, 384 Y/E, and 421 K/L reduce binding – paradoxically, this Fab was retrieved from the library after

masking with known anti-CD4BS MAbs – binding is sensitive to deglycosylation – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure, antibody sequence variable domain**)

- No.** 1195  
**MAb ID** L42  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp120 CD4BS  
**References** Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995  
**Keywords** antibody binding site definition and exposure, review
- L42: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
  - L42: Substitutions at 257 T/R, 368 D/R, 370 E/R, 266 A/E and 477 D/V reduce binding – binding was significantly enhanced by 381 E/P and 382 F/L – binding is sensitive to deglycosylation – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure**)

- No.** 1196  
**MAb ID** L52  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp120 CD4BS  
**References** Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995  
**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, review
- L52: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
  - L52: Binding is sensitive to deglycosylation – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure, antibody sequence variable domain**)

- No.** 1197  
**MAb ID** L72  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen**

- Species (Isotype)** mouse  
**Ab Type** gp120 CD4BS  
**Research Contact** Dr. Hariharam, IDEC Pharmaceuticals Corp  
 La Jolla, CA  
**References** Ditzel *et al.* 1997
- L72: Used to bind gp120 to solid phase to select MAbs from a phage selection library. Ditzel *et al.* [1997]

- No.** 1198  
**MAb ID** M12  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 CD4BS  
**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD  
**References** Sugiura *et al.* 1999; Earl *et al.* 1994
- M12 database comment: There is a p15 and a gp120 mouse MAb both called M12 and a human gp41 Fab M12.
  - M12: A comparison of 25 gp120 specific, conformation dependent MAbs was done – M12 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4 – 50% neutralization of NL4-3 was achieved with 21 ug/ml of M12. Sugiura *et al.* [1999]
  - M12: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

- No.** 1199  
**MAb ID** M13  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 CD4BS  
**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD  
**References** Sugiura *et al.* 1999; Earl *et al.* 1994
- M13: A comparison of 25 gp120 specific, conformation dependent MAbs was done – M13 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4 – 50% neutralization of NL4-3 was achieved with 35 ug/ml of M13. Sugiura *et al.* [1999]



- M13: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1200  
**MAb ID** M6  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 CD4BS  
**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD  
**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- M6: A comparison of 25 gp120 specific, conformation dependent MAbs was done – M6 is part of a group of MAbs labeled A1 – all A1 MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, blocked CD4 binding, were sensitive to mutations in gp120 positions 368 and 370 that directly contact CD4. Sugiura *et al.* [1999]
- M6: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1201  
**MAb ID** MAG 116  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 CD4BS  
**Research Contact** C. Y. Kang, IDEC Inc  
**References** Kang *et al.* 1994

- MAG 116: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R, 368 D/R or T, 370 E/R or Q, 384 Y/E, 421 K/L – neutralizes MN, IIIB and RF. Kang *et al.* [1994]

**No.** 1202  
**MAb ID** MAG 12B  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 CD4BS  
**Research Contact** C. Y. Kang, IDEC Inc  
**References** Kang *et al.* 1994

- MAG 12B: Amino acid substitutions that reduce binding 10 fold: 257 T/R, 368 D/R or T, 370 E/R or Q, 384 Y/E, 477 D/V – weak neutralization of IIIB. Kang *et al.* [1994]

**No.** 1203  
**MAb ID** MAG 29B  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 CD4BS  
**Research Contact** C. Y. Kang, IDEC Inc  
**References** Kang *et al.* 1994

- MAG 29B: Amino acid substitutions that reduce binding 10 fold: 257 T/R, 368 D/R or T, 370 E/R or Q, 384 Y/E, 386 N/Q, 421 K/L – weak neutralization of IIIB. Kang *et al.* [1994]

**No.** 1204  
**MAb ID** MAG 3B  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 CD4BS  
**Research Contact** C. Y. Kang, IDEC Inc  
**References** Kang *et al.* 1994

- MAG 3B: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R or A or G, 262 N/T, 368 D/R or T, 370 E/R or Q, 381 E/P, 384 Y/E, 421 K/L, 475 M/S, 477 D/V. Kang *et al.* [1994]

**No.** 1205  
**MAb ID** MAG 55 (#55)  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120  
**Species (Isotype)** mouse  
**Ab Type** gp120 CD4BS  
**Research Contact** C. Y. Kang, IDEC Inc  
**References** Koefoed *et al.* 2005; Moore & Sodroski 1996; Kang *et al.* 1994  
**Keywords** antibody binding site definition and exposure

- MAG 55: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. MAG 55 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a CD4BS epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- MAG 55: Called #55 – binding reciprocally inhibited by other anti-CD4 binding site MAbs, and by some C1-C5 MAbs – binding enhanced by anti-V3 MAb 110.5 and anti-V2 MAbs G3-136 and G3-4 – enhances binding of many anti-V3 and -V2 MAbs. Moore & Sodroski [1996]
- MAG 55: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R, 368 D/R or T, 370 E/R or Q, 384 Y/E, 421 K/L, 470 P/L, 475 M/S, 477 D/V – neutralizes MN, IIIB and RF. Kang *et al.* [1994]

No. 1206

MAB ID MAG 72 (L72)

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing L

Immunogen vaccine

Vector/Type: sCD4-gp120 complex Strain:  
B clade HXB2 HIV component: gp120

Species (Isotype) mouse

Ab Type gp120 CD4BS

Research Contact C. Y. Kang or Dr. Hariharam, IDEC Pharmaceuticals Corp, La Jolla, CA

References Ditzel *et al.* 1997; Kang *et al.* 1994

- MAG 72: Called L72 – used to bind gp120 to solid phase to select MAbs from a phage selection library. Ditzel *et al.* [1997]
- MAG 72: Amino acid substitutions that reduce binding 10 fold: 257 T/R or A or G, 262 N/T, 368 D/R or T, 370 E/R or Q, 384 Y/E, 421 K/L, 477 D/V – neutralizes MN, IIIB and RF. Kang *et al.* [1994]

No. 1207

MAB ID MAG 86

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing L

Immunogen vaccine

Vector/Type: sCD4-gp120 complex Strain:  
B clade HXB2 HIV component: gp120

Species (Isotype) mouse

Ab Type gp120 CD4BS

Research Contact C. Y. Kang, IDEC Inc

References Kang *et al.* 1994

- MAG 86: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R, 368 D/R or T, 370 E/R or Q, 384 Y/E, 421 K/L, 470 P/L, 477 D/V – neutralizes MN, IIIB and RF. Kang *et al.* [1994]

No. 1208

MAB ID MAG 96

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing L

Immunogen vaccine

Vector/Type: sCD4-gp120 complex Strain:  
B clade HXB2 HIV component: gp120

Species (Isotype) mouse

Ab Type gp120 CD4BS

Research Contact C. Y. Kang, IDEC Inc

References Koefoed *et al.* 2005; Kang *et al.* 1994

Keywords antibody binding site definition and exposure

- MAG 96: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. MAG 96 was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a CD4BS epitope. Koefoed *et al.* [2005] (**antibody binding site definition and exposure**)
- MAG 96: Amino acid substitutions that reduce binding 10 fold: 256 S/Y, 257 T/R, 368 D/R or T, 370 E/R – weak neutralization of IIIB. Kang *et al.* [1994]

No. 1209

MAB ID MTW61D

HXB2 Location Env

Author Location gp120 (W61D)

Epitope

Neutralizing L

Immunogen HIV-1 infection

Species (Isotype) human

Ab Type gp120 CD4BS

References Gorny & Zolla-Pazner 2004; Fouts *et al.* 1998; Sullivan *et al.* 1998a

Keywords enhancing activity, review

- MTW61D: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- MTW61D – the HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – Fab fragment MTW61D also enhances YU2 entry, ruling out Fc interactions or Env cross-linking as a mechanism, while neutralizing HXBc2 – MTW61D was obtained by panning libraries derived from bone marrow from a long term asymptomatic donor against gp120 from primary isolate W61D. Sullivan *et al.* [1998a] (**enhancing activity**)

No. 1210

MAB ID S1-1

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing L

Immunogen HIV-1 infection

Species (Isotype) human (IgG1λ)

Ab Type gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Wisniewski *et al.* 1996; Moran *et al.* 1993; Lake *et al.* 1992

**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, complement, enhancing activity, review

- S1-1: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- S1-1: S1-1 is V H1 – V-region heavy chain usage was examined and a bias of enhanced V H1 and V H4, and reduced V H3, was noted among HIV infected individuals. Wisniewski *et al.* [1996] (**antibody sequence variable domain**)
- S1-1: Heavy (V H1) and light (V lambdaIII) chain sequenced – no enhancing activity – similar germline sequence to MAb 86, but very different activity. Moran *et al.* [1993] (**enhancing activity, antibody sequence variable domain**)
- S1-1: Neutralizes IIIB and MN without complement, and neutralizes RF and a clinical isolate with complement – binds to native but not denatured gp120 – inhibits sCD4-gp120 binding. Lake *et al.* [1992] (**antibody binding site definition and exposure, complement**)

**No.** 1211

**MAB ID** T13

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- T13: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T13 is one of three MAbs labeled group Cb, that was type-specific for BH8 – T13 fully blocked CD4 binding, and the deletion of the V3 loop enhanced binding 10-fold. Sugiura *et al.* [1999]
- T13: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1212

**MAB ID** T49

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- T49: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T49 is one of three MAbs labeled group Cb, that was type-specific for BH8 – T49 fully blocked CD4 binding, and the deletion of the V3 loop enhanced binding 10-fold. Sugiura *et al.* [1999]
- T49: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1213

**MAB ID** T56

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 CD4BS

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- T56: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T56 is one of three MAbs labeled group Cb, that was type-specific for BH8 – T56 fully blocked CD4 binding, and the deletion of the V3 loop enhanced binding 10-fold. Sugiura *et al.* [1999]
- T56: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1214

**MAB ID** TH9

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen**

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 CD4BS

**Research Contact** Michael Fung, Tanox Biosystem, USA

**References** Gorny & Zolla-Pazner 2004; Yang *et al.* 1998; D'Souza *et al.* 1995

**Keywords** assay development, review, subtype comparisons, variant cross-recognition or cross-neutralization

- TH9: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this MAb, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- TH9: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998] (**assay development**)

- TH9: Found to neutralize MN, but not JRC5F, two B subtype primary isolates, or a D subtype primary isolate, by most labs in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1215

**MAb ID** anti-CD4BS summary

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)**

**Ab Type** gp120 CD4BS

**References** Moore & Sodroski 1996; Thali *et al.* 1993

- Anti-CD4 binding site antibodies (CD4BS) competitively inhibit CD4 binding to monomeric gp120, and they differ in precise dependence on gp120 residues, but generally require Asp-368 and Glu-370. Moore & Sodroski [1996]
- Shared components of MAb epitopes and the discontinuous CD4 binding regions included Thr 257, Asp 368, Glu 370, Lys 421 through Trp 427 and Asp 457. Thali *et al.* [1993]

No. 1216

**MAb ID** b11

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Parren *et al.* 1998a

**Keywords** binding affinity, review

- b11: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- b11: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)

No. 1217

**MAb ID** b13

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Parren & Burton 1997; Parren *et al.* 1998a; Parren *et al.* 1995

**Keywords** binding affinity, immunoprophylaxis, review

- b13: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- b13: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)
- b13: Fab b13 was used as a control in a hu-PBL SCID mouse study – animals were protected from HIV-1 SF2 infection by IgG1b12, somewhat by Fab b12, but not by b13. Parren *et al.* [1995]; Parren & Burton [1997] (**immunoprophylaxis**)

No. 1218

**MAb ID** b14

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Gorny & Zolla-Pazner 2004; Parren *et al.* 1998a

**Keywords** binding affinity, review

- b14: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- b14: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)

No. 1219

**MAb ID** b3

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**References** Selvarajah *et al.* 2005; Pantophlet *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Pantophlet *et al.* 2003a; Parren *et al.* 1998a; Parren *et al.* 1997b

**Keywords** antibody binding site definition and exposure, antibody interactions, binding affinity, review, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- b3: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4BS MAbs except Fab b12 (b6, b3, F105) did not bind to either GDMR or mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- b3: This review summarizes MAbs directed to HIV-1 Env. There are 51 CD4BS MAbs and Fabs in the database; most, like this Fab, neutralize TCLA strains only. Gorny & Zolla-Pazner [2004] (**review**)
- b3: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including b3. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- b3: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 binding to those that affect binding of sCD4 and two non-neutralizing anti-CD4BS Abs b3 and b6 – while the epitope maps overlapped, there were some differences observed – binding of CD4 was never enhanced, indicating it had evolved to be optimal – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished – 2G12 binding was largely unperturbed, indicating these proteins were not grossly misfolded. Pantophlet *et al.* [2003a] (**antibody binding site definition and exposure**)
- b3: A gp120 molecule was design to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- b3: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet

(C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

- b3: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)
- b3: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

No. 1220

**MAb ID** b6

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** N

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CD4BS

**Research Contact** Dennis Burton, Scripps, San Diego, CA, USA

**References** Law *et al.* 2007; Dey *et al.* 2007; Selvarajah *et al.* 2005; Pantophlet *et al.* 2004; Binley *et al.* 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Pantophlet *et al.* 2003a; Pognard *et al.* 2003; Kwong *et al.* 2002; Parren *et al.* 1998a; Parren *et al.* 1997b

**Keywords** antibody binding site definition and exposure, antibody interactions, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- b6: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP trimers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. 17b binding was induced similarly by CD4 for the WT and stabilized forms. Non-neutralizing MAbs PA-1 (V3) and b6 (CD4BS)

- bound less efficiently to the stabilized trimer. Dey *et al.* [2007] (**vaccine antigen design**)
- b6: G1 and G2 recombinant gp120 proteins, consisting of 2F5 and 4E10, and 4E10 epitopes, respectively, engrafted into the V1/V2 region of gp120, were tested as an immunogen to see if they could elicit MPER antibody responses. Deletion of V1/V2 from gp120 or its replacement with G1 and G2 grafts reduced the affinity for b6, however shortening of the N and C termini of the V3 loop did not greatly affect binding. Law *et al.* [2007] (**vaccine antigen design**)
  - b6: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4BS MAbs except Fab b12 (b6, b3, F105) did not bind to either GDMR or mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
  - b6: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. b6 was included as an example of a CD4BS antibody that is not strongly neutralizing, and it only was able to neutralize a few highly sensitive primary viruses and T-cell adapted viral strains that were B clade. Steric restrictions probably block its binding site in most isolates. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
  - b6: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including b6. Pantophlet *et al.* [2004] (**vaccine antigen design**)
  - b6: Alanine scanning mutagenesis was used to compare substitutions that affected anti-CD4BS NAb b12 binding to those that affect binding of sCD4 and two non-neutralizing anti-CD4BS Abs b3 and b6 – while the epitope maps overlapped, there were some differences observed – binding of CD4 was never enhanced, indicating it had evolved to be optimal – rec gp120s were engineered to contain combinations of Alanine substitutions that enhanced b12 binding, and while binding of b12 to these gp120 monomers was generally maintained or increased, binding by five non-neutralizing anti-CD4bs MAbs (b3, b6, F105, 15e, and F91) was reduced or completely abolished – 2G12 binding was largely unperturbed, indicating these proteins were not grossly misfolded. Pantophlet *et al.* [2003a]
  - b6: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
  - b6: Virion capture assays are not a good predictor of neutralization, and the presentation of epitopes using this assay seems to be different from that of functional Envelope spikes on primary isolates – F105 and b6 could efficiently block the b12-mediated capture of infectious virions in a virus capture, but did not inhibit b12 neutralization – while b12 was potent at neutralizing the three primary virions JR-CSF, ADA, and 89.6, the Abs F105, 19b, and Fab b6 were overall very poor neutralizers. Poignard *et al.* [2003]
  - b6: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the CD4BS MAbs used. Zwick *et al.* [2003] (**antibody interactions**)
  - b6: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
  - b6: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
  - b6: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b]

No. 1221

MAb ID polyclonal

**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* CD4BS, Gag, V3

**Species (Isotype)** mouse

**Ab Type** gp120 CD4BS

**References** Truong *et al.* 1996

- Antibodies raised against recombinant anti-p55 virus-like particles with the p24 region 196-226 deleted, bearing inserts of either the V3 or the CD4BS regions of gp120 were studied – no neutralizing responses, weak Env and strong Gag responses were elicited – the major homology region (MHR) and proximal sequences was found to be required for capsid assembly. Truong *et al.* [1996]

**No.** 1222

**MAB ID**

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** yes

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 CD4BS, gp120 CD4i, gp120 V2, gp120 V3

**References** Moore *et al.* 2001

- Moore and colleagues review structural aspects of gp120 and how they relate to antigenic domains, and review the data concerning the lack of a clear relationship between genetic subtype and serotype – they suggest the primary goal in vaccine efforts should be to design an immunogen that can be shown to elicit neutralizing antibodies against a significant proportion of primary isolates – assay artifacts that can result in confused interpretations are also discussed, such as Ab binding to defective spikes, which does not affect HIV-1 infectivity, but can dominant an assay signal. Moore *et al.* [2001]

**No.** 1223

**MAB ID** 17b (1.7b, sCD4-17b)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L P (wea

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4i, gp120 CCR5BS

**Research Contact** James Robinson, Tulane University, New Orleans, LA, USA

**References** Cham *et al.* 2006; Choudhry *et al.* 2006; Holl *et al.* 2006a; Huang *et al.* 2007a; Kothe *et al.* 2007; Dey *et al.* 2007; Choudhry *et al.* 2007; Billington *et al.* 2007; Liao *et al.* 2006; Dorfman *et al.* 2006; Selvarajah *et al.* 2005; Martín-García *et al.* 2005; Lusso *et al.* 2005; Koefoed *et al.* 2005; Haynes *et al.* 2005; Pinter *et al.* 2004; Pantophlet *et al.* 2004;

Nabatov *et al.* 2004; McCaffrey *et al.* 2004; Ling *et al.* 2004; Liao *et al.* 2004; Biorn *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Zhu *et al.* 2003; Ohagen *et al.* 2003; Xiang *et al.* 2003; Labrijn *et al.* 2003; Enshell-Seijffers *et al.* 2003; Dey *et al.* 2003; Choe *et al.* 2003; Cavacini *et al.* 2003; Binley *et al.* 2003; He *et al.* 2003; Ling *et al.* 2002; Finnegan *et al.* 2002; Cavacini *et al.* 2002; Arthos *et al.* 2002; Zhang *et al.* 2002; Basmaciogullari *et al.* 2002; Grundner *et al.* 2002; Edwards *et al.* 2002; Xiang *et al.* 2002a; Xiang *et al.* 2002b; Dowd *et al.* 2002; Yang *et al.* 2002; Schulke *et al.* 2002; Golding *et al.* 2002b; Srivastava *et al.* 2002; Kwong *et al.* 2002; Finnegan *et al.* 2001; Poignard *et al.* 2001; Zhang *et al.* 2001a; York *et al.* 2001; Kolchinsky *et al.* 2001; Si *et al.* 2001; Rizzuto & Sodroski 2000; Yang *et al.* 2000; Stamatatos *et al.* 2000; Salzwedel *et al.* 2000; Park *et al.* 2000; Ly & Stamatatos 2000; Grovit-Ferbas *et al.* 2000; Binley *et al.* 1999; Hoffman *et al.* 1999; Oscherwitz *et al.* 1999a; Stamatatos & Cheng-Mayer 1998; Binley *et al.* 1998; Sullivan *et al.* 1998a; Sullivan *et al.* 1998b; Rizzuto *et al.* 1998; Moore & Binley 1998; Wyatt *et al.* 1998; Kwong *et al.* 1998; Parren *et al.* 1997b; Wyatt *et al.* 1997; Cao *et al.* 1997b; Ditzel *et al.* 1997; Weinberg *et al.* 1997; Li *et al.* 1997; Fouts *et al.* 1997; Binley *et al.* 1997a; Trkola *et al.* 1996a; Wu *et al.* 1996; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Wyatt *et al.* 1995; Beretta & Dalgleish 1994; Thali *et al.* 1994; Moore *et al.* 1993c; Thali *et al.* 1993

**Keywords** antibody binding site definition and exposure, antibody interactions, binding affinity, brain/CSF, co-receptor, computational epitope prediction, dendritic cells, immunoprophylaxis, immunotherapy, kinetics, mimotopes, neutralization, review, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 17b database comment: 48d and 17b have similar epitopes, and the pair are unique among human and rodent MABs. (**antibody binding site definition and exposure**)
- 17b: NIH AIDS Research and Reference Reagent Program: 4091.
- 17b: This Ab was found to be able to bind to a highly stable trimeric rgp140 derived from a HIV-1 subtype D isolate containing intermonomer V3-derived disulfide bonds and lacking gp120/gp41 cleavage. Protein disulfide isomerase treatment of rgp120 and rgp140 was found to severely inhibit binding of 17b, suggesting a structural need for V3-derived disulfide bonds in coreceptor binding. gp140 binding to 17b was 2-fold enhanced with by sCD4, indicating the proteolytically

immature protein was able to undergo CD4i conformational changes. Billington *et al.* [2007] (**antibody binding site definition and exposure**)

- 17b: SOSIP Env proteins are modified by the introduction of a disulfide bond between gp120 and gp41 (SOS), and an I559P (IP) substitution in gp41, and form trimers. The KNH1144 subtype A virus formed more stable trimers than did the prototype subtype B SOSIP Env, JRFL. The stability of gp140 trimers was increased for JR-FL and Ba-L SOSIP proteins by substituting the five amino acid residues in the N-terminal region of gp41 with corresponding residues from KNH1144 virus. b12, 2G12, 2F5, 4E10 and CD4-IgG2 all bound similarly to the WT and to the stabilized JRFL SOSIP trimers, suggesting that the trimer-stabilizing substitutions do not impair the overall antigenic structure of gp140 trimers. 17b binding was induced similarly by sCD4 in the WT and stabilized forms. Non-neutralizing MAbs PA-1 and b6 bound less efficiently to the stabilized trimer. Dey *et al.* [2007] (**vaccine antigen design**)
- 17b: The small molecule HIV-1 entry inhibitor IC9564 significantly enhanced binding of 17b Ab to gp120 on cell surface and on viral particles. The binding was independent of the presence of soluble CD4 suggesting that IC9564 induces conformational change in gp120 that exposes the concealed 17b epitope. Significant increase in neutralizing activity of 17b in the presence of IC9564 was observed for NLDH120 and NL4-3 virus strains. In contrast to CD4, IC9564 does not induce a conformational change in gp41, and inhibits CD4-induced gp41 conformational changes. Huang *et al.* [2007a] (**antibody binding site definition and exposure**)
- 17b: Four consensus B Env constructs: full length gp160, uncleaved gp160, truncated gp145, and N-linked glycosylation-site deleted (gp160-201N/S) were compared. All were packaged into virions, and all but the fusion defective uncleaved version mediated infection using the CCR5 co-receptor. CD4 inducible MAbs 17b and E51 were tested for the ability to neutralize the various forms of Con B; as anticipated gp160 and gp145 were not neutralized by these two MAbs, but the gp160-201N/S mutant was neutralized with IC50 values of 10 ug/ml, suggesting increased formation and/or exposure of the co-receptor binding site. The poorly infectious clone WITO4160.27 was also somewhat susceptible to neutralization by these clones. Kothe *et al.* [2007] (**vaccine antigen design, variant cross-recognition or cross-neutralization**)
- 17b: Cloned Envs (clades A, B, C, D, F1, CRF01\_AE, CRF02\_AG, CRF06\_cpx and CRF11\_cpx) derived from donors either with or without broadly cross-reactive neutralizing antibodies were shown to be of comparable susceptibility to neutralization by 17b. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 17b: Neutralization of HIV-1 primary isolates from clade B by different formats of 17b was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of 17b in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor, neutralization, variant cross-recognition or cross-neutralization**)
- 17b: The CDR3 regions of CD4i Abs (E51, 412d, 17b, C12 and 47e) were cloned onto human IgG1 and tested for their ability to inhibit CCR5 binding. Only E51 successfully immunoprecipitated gp120. Dorfman *et al.* [2006] (**co-receptor**)
- 17b: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 17b: The gp140 $\delta$ CFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. Both CD4 induced and A32 induced 17b was shown to bind specifically to all recombinant proteins except for the gp140 $\delta$ FI derived from subtype C virus. This Ab also bound specifically to one of the two tested subtype B gp120 proteins. The specific binding of his Ab to CON-S indicated that its conformational epitope was intact. Liao *et al.* [2006] (**antibody binding site definition and exposure, vaccine antigen design, subtype comparisons**)
- 17b: Called 1.7B. Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 1.7B has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)
- 17b: IgG antibody phage display libraries were created from HIV-1 + individuals after pre-selection of PBMC with gp120, as an alternative to using bone marrow for generating libraries. 17b was among a set of Abs used for competition studies to define the binding sites of the newly isolated MAbs, representing a MAb with a CD4i epitope. Koefoed *et al.* [2005]
- 17b: The epitope for the MAb D19 is conserved and embedded in V3. D19 is unique in that for R5 viruses, it was cryptic and did not bind without exposure to sCD4, and for X4 and R5X4 isolates it was constitutively exposed. D19b is unique among CD4i antibodies in that it binds to the V3 loop. CD4i MAbs 17b and 48d were used as controls for CD4i characterization; in contrast to D19, other CD4i MAbs bind to the conserved bridging sheet and do not differentiate between R5 and X4 using strains. 17b, like D19, was able to neutralize the BaL isolate only in combination with sCD4. Lusso *et al.* [2005]
- 17b: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using F105, IgG1b12, 17b and 48d, 2G12 and 447-52D. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Martín-García *et al.* [2005]



- 17b: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4i MAb (48d, 17b) did not bind to either GDMR or mCHO even with sCD4. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- 17b: The peptide 12p1 (RINNIPWSEAMM) inhibits direct binding of YU2 gp120 or Env trimer to CD4, CCR5 and MAb 17b in a concentration-dependent allosteric manner. 12p1 is thought to bind to unbound gp120 near the CD4 binding site, with a 1:1 stoichiometry. 12p1 also inhibited MAb F105 binding presumably because F105 favors an unactivated conformation, but not MAbs 2G12 or b12. The 1:1 stoichiometry, the fact that the peptide binding site is accessible on the trimer, the non-CD4 like aspect of the binding, and an ability to inhibit viral infection in cell cultures make it a promising lead for therapeutic design. Biorn *et al.* [2004]
- 17b: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, review**)
- 17b: A32-rgp120 complexes opened up the CCR5 co-receptor binding site, but did not induce neutralizing antibodies with greater breadth among B subtype isolates than did uncomplexed rgp120 in vaccinated guinea pigs. 17b was used as a control to show A32-bound rgp120 had enhanced binding to this CD4-inducible MAb. Liao *et al.* [2004] (**vaccine antigen design**)
- 17b: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b was decreased by trypsin, but increased by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 17b: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) and two sites adjacent to V3, C2 (GM292 C2) and (GM329 C3), increased neutralization susceptibility to CD4i Fab X5, but each of the glycan mutants and SF162 were refractive to neutralization with 48d and 17b. The loss of sites in C4 (GM438 C4), or V5 (GM454 V5) did not increase neutralization susceptibility to Fab X5. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure, vaccine antigen design**)
- 17b: A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4, R5, and X4 viruses were generated, and sCD4, 2G12 and b12 neutralization resistance patterns were modified by addition of the late stage V1V2, glycosylation changes, and charge in concert, while neutralization by 2F5 was unaffected. 15e, 17b, and 48d could not neutralize any of the variants tested. Nabatov *et al.* [2004] (**antibody binding site definition and exposure, co-receptor**)
- 17b: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 17b. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- 17b: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12 which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three CD4i MAbs were tested; all preferentially neutralized SF162, and JRFL became neutralization sensitive to CD4i Abs if the SF162 V1V2 loop was exchanged. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 17b: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. CD4i Abs 17b and X5 were weakly neutralizing in all formats, WT, SOS, and when added postbinding. Binley *et al.* [2003] (**vaccine antigen design**)
- 17b: Called 1.7b. The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. B4e8 enhanced binding of CD4i MAbs 4.8d, 1.7b, and A1g8 to R5X4 virus 92HT593, but only of 48d to the R5 virus 92US660, and there was only a modest impact of the combination of B4e8 and CD4i MAbs on

- neutralization. Cavacini *et al.* [2003] (**antibody interactions, co-receptor**)
- 17b: 17b was used as a negative control to test CDR3 tyrosine sulfation of MAbs 47e, 412d, CM51, E51, C12 and Sb1, since its CDR3 tyrosines are buried. As expected, 17b did not incorporate sulfates while the other MAbs did. Thus, the expression of 17b, or its binding to gp120 bound to CD4-Ig, was not affected by sulfation-inhibition. In addition, 17b was used as a positive control to test whether MAbs 47e, 412d, E51, Sc1 and C12 are CD4i Abs. Binding efficiency of all MAbs to ADA gp120 was doubled in the presence of CD4, showing that they are CD4-induced. scFv 17b was shown to efficiently bind to gp120 of three R5 isolates and to the HXBc2 X4 isolate. Neutralization assays showed that 17b was less efficient at neutralizing primary R5 and R5X4 isolates than MAbs 412d and E51, however, it was more efficient at neutralizing X4 isolates than these MAbs. Choe *et al.* [2003] (**antibody binding site definition and exposure, neutralization**)
  - 17b: A sCD4-17b single chain chimera was made that can bind to the CD4 binding site, then bind and block co-receptor interaction. This chimeric protein is a very potent neutralizing agent, more potent than IgG1b12, 2G12 or 2F5 against Ba-L infection of CCR5-MAGI cells. It has potential for prophylaxis or therapy. It neutralized 5/6 R5 and X4 strains from the B clade, but was only moderately protective against a D clade isolate, and did not neutralize clade A, C, E, and F isolates. Dey *et al.* [2003] (**co-receptor, immunoprophylaxis, variant cross-recognition or cross-neutralization, immunotherapy, subtype comparisons**)
  - 17b: 17b is known to be comprised of elements from four discontinuous beta strands. Using 17b MAb to select peptides from a combinatorial library, and analyzing the peptides using a novel discontinuous epitope reconstruction program, enabled epitope prediction. Segments of gp120 were reconstructed as an antigenic protein mimetic recognized by 17b. Comparisons then were made with a similar prediction of contact residues for CG10, a CD4i MAb that competes with 17b, but has a distinct binding site. Enshell-Seijffers *et al.* [2003] (**antibody binding site definition and exposure, mimotopes, computational epitope prediction**)
  - 17b: Vaccination of a gp120-CD4 fusion complex in six transgenic XMG2 XenoMouse mice that produce human IgG2 with K light chain did not produce any neutralizing antibodies. 36/39 MAbs derived from one of these mice were in one of two competition groups that were conformational and specific for the complex, suggesting this chimeric vaccine may be of little value, as immunodominant responses recognized epitopes not present in native Env. MAbs from the two CD4-gp120 complex-specific competition groups did not compete with MAbs with known targets on HIV-1 gp120, but their binding was enhanced by binding of 17b. He *et al.* [2003]
  - 17b: This study shows the fragments of CD4i MAbs are better able to neutralize virus than whole IgG. Neutralization of HIV-1 R5 isolates JRFL, JR-CSF and ADA by CD4i MAbs X5, 17b, and 48d decreased with increased molecule size, the neutralizing potency of single-chain Fv (scFv) > than Fab fragments > whole Ab molecules. (With the exception of IgG 48d neutralization of HIV-1 ADA.) HIV-1 X4 isolates 89.6 and HxB2 are both relatively sensitive even to the larger IgG version. R5X4 isolate neutralization was dependent on the isolate and co-receptor usage. The CD4i MAb fragments neutralize HIV-1 subsequent to CD4 binding. The CD4i MAbs bind near the co-receptor binding sites on gp120. Co-receptors bind to the conserved beta19 strand and part of the V3 loop, regions that are masked by the V1V2 loops in the CD4-unbound state. When CD4 is bound, the co-receptor site is exposed near the membrane surface where it would be optimally accessible to co-receptors, and the smaller versions of the molecules are better able to overcome the steric hindrance. Labrijn *et al.* [2003] (**antibody binding site definition and exposure, co-receptor, variant cross-recognition or cross-neutralization**)
  - 17b: Env genes derived from uncultured brain biopsy samples from four HIV-1 infected patients with late-stage AIDS were compared to env genes from PBMC samples. Brain isolates did not differ in the total number or positions of N-glycosylation sites, patterns of coreceptor usage, or ability to be recognized by gp160 and gp41 MAbs. 17b recognized most variants, some from each of the four individuals, by gp120 immunoprecipitation. Ohagen *et al.* [2003] (**brain/CSF, variant cross-recognition or cross-neutralization**)
  - 17b: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
  - 17b: This paper describes the generation of CD4i MAb E51, that like CD4i MAb 17b, blocks CCR5 binding to sCD4-bound gp120. E51 has more cross-neutralizing potency than other prototype CD4i MAbs (17b) for B and C clade isolates. E51 and 17b both neutralized HIV-1 clade B strains HXBc2 and ADA, while JR-FL and 89.6 were only neutralized by E51, not 17b. Clade C strains MCGP1.3 and SA32 were both inhibited by 17b and E51, but E51 was more potent against SA32. The substitutions E381R, F383S, R419D I420R, K421D, Q422L, I423S, and Y435S (HXB2 numbering) all severely reduce 17b and E51 binding. All but I423S also diminish CCR5 binding by more than 50%. The mutation F383S also inhibits sCD4 binding and F105 binding, and K421D inhibits F105 binding, but not sCD4. Xiang *et al.* [2003] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons**)
  - 17b: The HIV-1 primary isolate DH012 has preserved the epitopes for the MAbs IgG1b12, 2G12, 17b, however natural DH012 infection in chimpanzees and DH012 gp120 vaccination in guinea pigs does not give rise to Abs against these epitopes. Zhu *et al.* [2003] (**vaccine-specific epitope characteristics**)
  - 17b: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2

- and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a CD4i MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- 17b: The two N-terminal domains of CD4, termed D1 and D2, when expressed in the absence of the remaining domains of CD4 retain the capacity to bind to gp120—coding sequences of D1D2 and Ig $\alpha$ p were fused to create a large, multivalent rec protein D1D2Ig $\alpha$ p, which, unlike CD4, does not enhance infection at sub-optimal concentrations—the MAb 17b can also enhance viral replication at sub-optimal concentrations, but D1D2-Ig $\alpha$  inhibited the 17b enhancement of two primary isolates. Arthos *et al.* [2002] (**variant cross-recognition or cross-neutralization**)
  - 17b: gp120 mutants were used to define the CXCR4 binding site using CXCR4 displayed on paramagnetic proteoliposomes (PMPLs) to reduce non-specific gp120 binding—basic residues in the V3 loop and the  $\beta$ 19 strand (RIKQ, positions 419–422) were involved, and deletion of the V1–V2 loops allowed CD4-independent CXCR4 binding—MAbs 17b (CD4i) and F105 (CD4BS) were used to study conformational changes in the mutants—the affinity of  $\Delta$ V1 and  $\Delta$ V1–V2 for 17b was dramatically increased and no longer inducible in the presence of sCD4—V3 mutants R298A and R327A were not recognized by 17b except in the presence of sCD4—mutations in the  $\beta$ 19 strand dramatically reduced 17b affinity in the presence or absence of sCD4, consistent with known 17b contact residues in this region. Basmaciogullari *et al.* [2002]
  - 17b: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-V3 MAb B4a1 increased binding of CD4i MAbs 48d, 17b and A1g8, but only A1g8 binding was increased by B4a1 to the R5 isolate. Additive effects on neutralization of the R5X4 isolate with B4a1 and CD4i MAbs was observed, presumably due to increased exposure of the CD4i binding site, but not for the R5 isolate. Anti-gp41 MAb F240 had a synergistic effect on neutralization with CD4i MAbs 48d and 17b, but not with A1g8 for the R5X4 virus. Cavacini *et al.* [2002] (**antibody interactions, co-receptor, variant cross-recognition or cross-neutralization**)
  - 17b: CD4 residue Phe43 significantly contributes to the affinity of CD4–gp120 interactions – despite decreased affinities for gp120, CD4 proteins and CD4-mimetic peptides lacking a Phe side-chain enhance binding of gp120 to 17b in a manner similar to Phe-bearing ligands indicating the Phe42 interaction is not critical for CD4-induced conformational changes in gp120. Dowd *et al.* [2002]
  - 17b: Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**vaccine-specific epitope characteristics**)
  - 17b: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I and Cluster II MAbs required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor, binding to a fusion intermediate. 17b was used to demonstrate that the Cluster I and II MAbs bound to gp120/gp41 complexes, not to gp41 after shedding of gp120. Finnegan *et al.* [2002]
  - 17b: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b. Golding *et al.* [2002b]
  - 17b: HIV-1 gp160 $\Delta$ CT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines—2F5 bound to gp160 $\Delta$ CT with a reconstituted membrane ten-fold better than the same protein on beads—anti-CD4BS MAbs IgG1b12 and F105, A32 (C1–C4), C11 (C1–C5), and 39F (V3) MAbs bound gp160 $\Delta$ CT PLs indistinguishably from gp160 $\Delta$ CT expressed on the cell surface—non-neutralizing MAbs C11 and A32 bound with lower affinity than NAb IgG1b12—the MAb 17b was sCD4 inducible on gp160 $\Delta$ CT PL. Grundner *et al.* [2002] (**vaccine antigen design**)
  - 17b: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
  - 17b: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb

- 17b. Ling *et al.* [2002] (**antibody binding site definition and exposure, co-receptor**)
- 17b: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140. Schulke *et al.* [2002] (**vaccine antigen design**)
  - 17b: Oligomeric gp140 (o-gp140) derived from R5 primary isolate US4 was characterized for use as a vaccine reagent – antigen capture ELISA was used to compare the antigenicity of gp120 and o-gp140 using a panel of well characterized MAbs – 17b recognized both gp120 monomer and o-gp140. Srivastava *et al.* [2002]
  - 17b: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91 was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**variant cross-recognition or cross-neutralization**)
  - 17b: Five CD4i MAbs were studied, 17b, 48d and three new MAbs derived by Epstein-Barr virus transformation of PBMC from an HIV+ long term non-progressor – 23e and 21c were converted to hybridomas to increase Ab production – all compete with the well-characterized 17b CD4i MAb in an ELISA antigen capture assay – critical binding residues are mapped and the CD4i MAb epitopes were distinct but share a common element near isoleucine 420, also important for CCR5 binding, and all five can block CCR5 binding to a sCD4-gp120 complex – the MAb 48d has the epitope most similar to the CCR5 binding site. Xiang *et al.* [2002a] (**antibody binding site definition and exposure**)
  - 17b: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibrin—stabilized oligomer gp140Δ683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002]
  - 17b: A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002]
  - 17b: Using a cell-fusion system, it was found CD4i antibodies 17b, 48d, and CG10 reacted faintly with Env expressing HeLa cells even in the absence of sCD4 or CD4 expressing target cells. Reactivity increased after sCD4 addition, but not after CD4 expressing target cell addition, and binding was not increased at the cell-to-cell CD4-Env interface. This suggests the CD4i co-receptor binding domain is largely blocked at the cell-fusion interface, and so CD4i antibodies would not be able access this site and neutralize cell-mediated viral entry. Finnegan *et al.* [2001]
  - 17b: Mutations in two glycosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYR-LINCNTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone—these same mutations tended to increase the neutralization sensitivity of the virus, including to 17b—only the CD4i antibodies 17b and 48d showed an increased affinity of the CD4 independent viruses relative to wild-type. Kolchinsky *et al.* [2001] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 17b: Structural aspects of the interaction of neutralizing Abs with HIV-1 Env are reviewed – Env essentially has three faces, one is largely inaccessible on the native trimer, and two that exposed but have low immunogenicity on primary viruses – neutralization is suggested to occur by inhibition of the interaction between gp120 and the target cell membrane receptors as a result of steric hindrance and it is noted that the attachment of approximately 70 IgG molecules per virion is required for neutralization, which is equivalent to about one IgG molecule per spike – the 2G12, 17b and b12 epitopes are discussed in detail – the 17b epitope is masked prior to CD4 binding by the V1-V2 loop and in contrast to sCD4, the binding of cell surface CD4 to virus does not appear to make the epitope accessible to binding by 17b to allow neutralization. Poignard *et al.* [2001] (**antibody binding site definition and exposure, review**)
  - SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkey's yielded highly pathogenic SHIV KU-1 – HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160 – substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1 – 17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
  - 17b: Abs against the V3 loop (50.1, 58.2, 59.1, 257-D, 268-D, 447-52D), CD4BS (IgG1b12, 559-64D, F105), CD4i (17b), and to gp41 (2F5, F240) each showed similar binding efficiency to Env derived from related pairs of primary and TCLA lines (primary: 168P and 320SI, and TCLA: 168C and 320SI-C3.3), but the TCLA lines were much more susceptible to neutralization suggesting that the change in TCLA lines that make them more susceptible to NAbs alters some step after binding – 17b bound at somewhat greater levels to 168C than to

- 168P, but this is not a general feature of 17b binding to primary versus TCLA strains. York *et al.* [2001] (**variant cross-recognition or cross-neutralization**)
- 17b: 17b binds to a CD4 inducible epitope which partially overlaps the CCR5 binding site – JRFL, YU2, 89.6, and HXB2 and their C1-, V1/V2-, C5 -deletion mutants were used to study how 17b binding affects gp120-CD4 interactions – 17b reduced CD4-gp120 interactions by decreasing the on-rate and increasing the off-rate of sCD4, while enhanced binding of sCD4 binding was observed for the 17b-bound, V1/V2 deleted gp120s – 17b was considered to be a surrogate for CCR5, and the authors suggest that 17b binding may shift V1/V2 into a position that interferes with CD4 binding, forcing a release. Zhang *et al.* [2001a] (**antibody binding site definition and exposure, kinetics**)
  - 17b: To determine the antigenicity of virus killed by thermal and chemical inactivation, retention of conformation-dependent neutralization epitopes was examined, and exposure of CD4BS epitopes was found to be enhanced (MAbs IgG1b12, 205-46-9, and 205-43-1) – binding to 2G12 and 447-52D epitopes was essentially unaltered – the 17b CD4i epitope was also exposed. Grovit-Ferbas *et al.* [2000] (**vaccine antigen design**)
  - 17b: SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000] (**variant cross-recognition or cross-neutralization**)
  - 17b: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000] (**antibody binding site definition and exposure**)
  - 17b: Mutagenesis defines Ile-420, Lys-421, Gln-422, Pro-438, and Gly-441 to be important residues for CCR5 binding – these positions are located on two strands that connect the gp120 bridging sheet and outer domain, suggesting a mechanism for conformational shifts induced by CD4 binding to facilitate CCR5 binding. Rizzuto & Sodroski [2000] (**antibody binding site definition and exposure**)
  - 17b: sCD4 can activate fusion between effector cells expressing Env and target cells expressing coreceptor (CCR5 or CXCR4) alone without CD4 – CD4i MAbs 17b and 48d have little effect on a standard cell fusion assay but potently block sCD4 activated fusion – 17b was broadly cross-reactive inhibiting sCD4 activated fusion with Env from clades A, B, C, D, E, F, and F/B. Salzwedel *et al.* [2000] (**subtype comparisons**)
  - 17b: Soluble gp140 derived from SF162, a neutralization-resistant primary isolate, and SF162AV2 a neutralization-susceptible isolate with 30 amino acids deleted from the V2 loop, were generated with or without the gp120-gp41 cleavage site intact – all forms are recognized by oligomer-specific MAb T4 and show enhanced binding of CD4i MAb 17b when sCD4 is bound – the fused forms are less efficiently recognized than the cleaved forms by polyclonal neutralizing sera from HIV-infected patients – the V3 loop is more exposed on the fused form. Stamatatos *et al.* [2000] (**vaccine antigen design**)
  - 17b: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000] (**vaccine antigen design**)
  - 17b: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**vaccine antigen design**)
  - 17b: A CD4-independent viral variant of IIIB, IIIBx, was generated on CXCR4-expressing cells – IIIBx exhibited greater exposure of the 17b and 48d epitopes and enhanced neutralization by CD4i MAbs and by polyclonal human sera – the 17b epitope has significant overlap with the CCR5 coreceptor binding site. Hoffman *et al.* [1999] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
  - 17b: A panel of MAbs was shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – CD4i MAbs 17b and 48d bound better to the deleted protein than to wild type. Binley *et al.* [1998] (**antibody binding site definition and exposure**)
  - 17b: 17b Fab was co-crystallized with a gp120 core and CD4, and its binding site can be directly visualized—17b binds to the “bridging sheet” of gp120, an antiparallel beta sheet region, contacting residues from the C4 region and the V1/V2

stem—the contact area is small for an Ab-antigen interactive surface, and dominated in the Ab by the heavy chain—the center of the binding region has hydrophobic interactions, and the periphery charge interactions, acidic on 17b and basic on gp120. Kwong *et al.* [1998] (**structure**)

- 17b: Moore and Binley provide a commentary on the papers by Rizzuto *et al.* [1998], Wyatt *et al.* [1998] and Kwong *et al.* [1998] – they point out 17b shares binding elements in gp120 with chemokine receptor molecules, and that CD4 needs to bind to gp120 first to make the 17b epitope accessible and it may be sterically blocked in the CD4 bound virus, thus making it a poor NAb for primary isolates Moore & Binley [1998]. Kwong *et al.* [1998]; Moore & Binley [1998]; Rizzuto *et al.* [1998]; Wyatt *et al.* [1998] (**review, structure**)
- 17b: Site directed mutagenesis of a WU2 protein with the V1-V2 loops deleted revealed key residues for 17b-gp120 interaction and interaction of gp120 and CCR5 – mutations in residues that reduced 17b by 70% were R/D 419, I/R 420, Q/L 422, Y/S 435, I/S 423, K/D 121 and K/D 421– 17b can neutralize HIV-1 strains that use different chemokine receptors, supporting a common region in gp120 in chemokine-receptor interaction. Rizzuto *et al.* [1998] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 17b: Deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V2 but not V1 enabled neutralization by CD4i MAbs 17b and 48d. Stamatatos & Cheng-Mayer [1998] (**antibody binding site definition and exposure, vaccine antigen design**)
- 17b: sCD4 induces 17b binding in primary isolates and TCLA strains – amino acids that reduce the efficiency of binding were determined and found also to compromise syncytia formation and viral entry – V1V2 deletion or sCD4 binding can expose the 17b epitope for both HXBc2 and macrophage tropic YU2 – neutralizing potency of 17b is probably weak due to poor exposure of the epitope – 17b epitope exposure upon sCD4 binding can occur over a wide range of temperatures, consistent with the energy of CD4 binding being sufficient to drive the V1/V2 loop into a new conformation. Sullivan *et al.* [1998b] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 17b: The HIV-1 virus YU2 entry can be enhanced by MAbs binding to the CD4BS, V3 loop, and CD4i epitopes – the activation for this enhanced entry state could be conferred on HxB2 by introducing the YU2 V3 loop, or the YU2 V3 and V1/V2 loops, and the presence of V1/V2 increased the enhancement – a similar effect is observed by sub-neutralizing concentrations of sCD4 and the effect is dependent of CCR5 – 17b enhances YU2 enhanced viral entry 10-fold, whereas HXBc2 was neutralized. Sullivan *et al.* [1998a]
- 17b: Summary of the implications of the crystal structure of a gp120 core bound to CD4 and 17b, combined with what is known about mutations that reduce NAb binding to gp120 – probable mechanism of neutralization is interference with chemokine receptor binding – mutations in 88N, 117K, 121K, 256S, 257T, N262, Delta V3, E370, E381, F 382, R 419, I 420, K 421, Q 422, I 423, W 427, Y 435, P 438, M 475 of HXBc2 (IIIB) reduce binding – the only variable residues in gp120 that contact 17b are 202T and 434M – the contact points for 17b with the crystallized incomplete gp120 are mostly in the heavy chain of the Ab, and there is a gap between 17b's light chain and the partial gp120 which may be occupied by the V3 loop in a complete gp120 molecule – the authors propose that the V2 and V3 loops may mask the CD4i Ab binding site, and that the V2 loop may be repositioned upon CD4 binding. Wyatt *et al.* [1998] (**structure**)
- 17b: Virus with the V1-V2 loop deleted was viable and more susceptible to neutralization by CD4i MAb 17b, and anti-V3 MAbs 1121, 9284, and 110.4, but not to a CD4BS MAb, F105, or sCD4. Cao *et al.* [1997b] (**vaccine antigen design**)
- 17b: Study shows neutralization is not predicted by MAb binding to JRFL monomeric gp120, but is associated with oligomeric Env binding – 17b bound monomer, oligomer, and neutralized JRFL in the presence of sCD4, but if sCD4 was not present, 17b only bound monomer. Fouts *et al.* [1997]
- 17b: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – 17b has synergistic response in combination with anti-V3 MAb 694/98-D. Li *et al.* [1997]
- 17b: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 17b: 48d binds to the IIIB protein and not IIIB V3 peptide, while binding to the Can0A V3 peptide, suggesting Can0A V3 is a conformer that mimics the 48d – it does not bind to 17b, distinguishing the epitopes. Weinberg *et al.* [1997]
- 17b: Binds to sgp120 efficiently, but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding – partial re-exposure if sCD4 was bound – could not bind to HXBc2 gp120 if the 19 C-term amino acids were deleted in conjunction with amino acids 31-93 in C1, but binding was restored in the presence of sCD4. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- 17b: Many MAbs inhibit binding (anti-C1, -C5, -C4, -CD4BS) – anti-V3 MAb 5G11 enhances binding, as do C1-C4 discontinuous epitopes A32 and 2/11c – enhances binding of some anti-V2 MAbs. Moore & Sodroski [1996] (**antibody interactions**)
- 17b: Binding did not result in significant gp120 dissociation from virion, in contrast to 48d, although the gp41 epitope of MAb 50-69 was exposed. Poignard *et al.* [1996a] (**antibody interactions**)
- 17b: Neutralizes JR-FL – inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a]
- 17b: MIP-1 $\alpha$  binding to CCR-5 expressing cells can be inhibited by gp120-sCD4 – binding of 17b blocks this inhibition. Wu *et al.* [1996]
- 17b: Binds with higher affinity to monomer and oligomer, slow association rate, poor neutralization of lab strain – this is in contrast to 48d, which has very different kinetics. Satten-tau & Moore [1995] (**kinetics, binding affinity**)
- 17b: Studies using a V1/V2 deletion mutant demonstrated that enhanced binding of 17b in the presence sCD4 involves the

V1/V2 loops, with more significant involvement of V2 – similar effect observed for 48d and A32. Wyatt *et al.* [1995] (**antibody binding site definition and exposure, vaccine antigen design**)

- 17b: A mutation in gp41, 582 A/T, confers resistance to neutralization (also confers resistance to MAbs F105, 48d, 21h and 15e). Thali *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 17b: Binding of 48d is much more influenced by sequence variation among molecular clones of LAI than is binding of 17b. Moore *et al.* [1993c] (**variant cross-recognition or cross-neutralization**)
- 17b: Epitope is better exposed upon CD4 binding to gp120 – competes with 15e and 21h, anti-CD4 binding site MAbs – 113 D/R, 252 R/W, 257 T/A or G, 370 E/D, 382 F/L, 420 I/R, 433A/L, 438 P/R and 475 M/S confer decreased sensitivity to neutralization. Thali *et al.* [1993] (**antibody binding site definition and exposure, antibody interactions**)

No. 1224

MAb ID 21c (2.1C)

HXB2 Location Env

Author Location gp120 (IIIB, J62)

Epitope

Subtype B

Neutralizing L

Immunogen HIV-1 infection

Species (Isotype) human (IgG)

Ab Type gp120 CD4i, gp120 CCR5BS

Research Contact James Robinson, Tulane University, New Orleans, LA, USA

References Haynes *et al.* 2005; Gorny & Zolla-Pazner 2004; Xiang *et al.* 2002b; Xiang *et al.* 2002a

Keywords antibody binding site definition and exposure, antibody generation, review, vaccine antigen design

- 21c: Called 2.1C. Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 2.1C has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)
- 21c: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 21c: Five CD4i MAbs were studied, 17b, 48d and three new MAbs derived by Epstein-Barr virus transformation of PBMC from an HIV+ long term non-progressor – 23e and 21c were converted to hybridomas to increase Ab production – all compete with the well-characterized 17b CD4i MAb in an ELISA antigen capture assay – critical binding residues are mapped and the CD4i MAb epitopes were distinct but share a common element near isoleucine 420, also important for CCR5 binding, and all five can block CCR5 binding to a sCD4-gp120 complex – the MAb 48d has the epitope most similar to the

CCR5 binding site. Xiang *et al.* [2002a] (**antibody binding site definition and exposure, antibody generation**)

- 21c: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure, vaccine antigen design**)

No. 1225

MAb ID 23e

HXB2 Location Env

Author Location gp120 (IIIB, J62)

Epitope

Subtype B

Neutralizing L

Immunogen HIV-1 infection

Species (Isotype) human (IgG)

Ab Type gp120 CD4i

Research Contact James Robinson, Tulane University, New Orleans, LA, USA

References Gorny & Zolla-Pazner 2004; Xiang *et al.* 2002b; Xiang *et al.* 2002a

Keywords antibody binding site definition and exposure, antibody generation, review, vaccine antigen design

- 23e: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 23e: Five CD4i MAbs were studied, 17b, 48d and three new MAbs derived by Epstein-Barr virus transformation of PBMC from an HIV+ long term non-progressor – 23e and 21c were converted to hybridomas to increase Ab production – all compete with the well-characterized 17b CD4i MAb in an ELISA antigen capture assay – critical binding residues are mapped and the CD4i MAb epitopes were distinct but share a common element near isoleucine 420, also important for CCR5 binding, and all five can block CCR5 binding to a sCD4-gp120 complex – the MAb 48d has the epitope most similar to the CCR5 binding site. Xiang *et al.* [2002a] (**antibody binding site definition and exposure, antibody generation**)
- 23e: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the

YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure, vaccine antigen design**)

**No.** 1226

**MAb ID** 48d (4.8d, 4.8D)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L P (wea

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 CD4i

**Research Contact** James Robinson, Tulane University, New Orleans, LA, USA

**References** Cham *et al.* 2006; Holl *et al.* 2006a; Selvarajah *et al.* 2005; Martín-García *et al.* 2005; Lusso *et al.* 2005; Pinter *et al.* 2004; Pantophlet *et al.* 2004; Nabatov *et al.* 2004; McCaffrey *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2003; Labrijn *et al.* 2003; Choe *et al.* 2003; Cavacini *et al.* 2003; Cavacini *et al.* 2002; Zhang *et al.* 2002; Edwards *et al.* 2002; Xiang *et al.* 2002a; Xiang *et al.* 2002b; Yang *et al.* 2002; Golding *et al.* 2002b; Kwong *et al.* 2002; Finnegan *et al.* 2001; Verrier *et al.* 2001; Kolchinsky *et al.* 2001; Salzwedel *et al.* 2000; Yang *et al.* 2000; Park *et al.* 2000; Ly & Stamatatos 2000; Fortin *et al.* 2000; Hoffman *et al.* 1999; Oscherwitz *et al.* 1999a; Stamatatos & Cheng-Mayer 1998; Binley *et al.* 1998; Yang *et al.* 1998; Sullivan *et al.* 1998b; Parren *et al.* 1998a; Mondor *et al.* 1998; Wyatt *et al.* 1998; Frankel *et al.* 1998; Parren *et al.* 1997b; Wyatt *et al.* 1997; Ugolini *et al.* 1997; Lee *et al.* 1997; Weinberg *et al.* 1997; Li *et al.* 1997; Binley *et al.* 1997a; Trkola *et al.* 1996a; Poignard *et al.* 1996a; Moore & Sodroski 1996; Sattentau & Moore 1995; Sattentau *et al.* 1995; Wyatt *et al.* 1995; Sattentau 1995; D'Souza *et al.* 1995; Moore *et al.* 1994b; Thali *et al.* 1994; Moore *et al.* 1993c; Moore & Ho 1993; Thali *et al.* 1993

**Keywords** antibody binding site definition and exposure, antibody interactions, binding affinity, co-receptor, dendritic cells, kinetics, neutralization, review, structure, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics, variant cross-recognition or cross-neutralization

- 48d database comment: 48d and 17b have similar epitopes, and the pair are unique among human and rodent MAbs.
- 48d: NIH AIDS Research and Reference Reagent Program: 1756.

- 48d: This Ab was shown to infrequently neutralize cloned Envs (clades A, B, C, D, F1, CRF01\_AE, CRF02\_AG, CRF06\_cpx and CRF11\_cpx) derived from donors with and without broadly cross-reactive neutralizing antibodies. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 4.8d: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 48d: The epitope for the MAb D19 is conserved and embedded in V3. D19 is unique in that for R5 viruses, it was cryptic and did not bind without exposure to sCD4, and for X4 and R5X4 isolates it was constitutively exposed. D19b is unique among CD4i antibodies in that it binds to the V3 loop. CD4i MAbs 17b and 48d were used as controls for CD4i characterization; in contrast to D19, other CD4i MAbs bind to the conserved bridging sheet and do not differentiate between R5 and X4 using strains. Lusso *et al.* [2005]
- 48d: The HIV-1 Bori-15 variant was adapted from the Bori isolate for replication microglial cells. Bori-15 had increased replication in microglial cells and a robust syncytium-forming phenotype, ability to use low levels of CD4 for infection, and increased sensitivity to neutralization by sCD4 and 17b. Four amino acid changes in gp120 V1-V2 were responsible for this change. Protein functionality and integrity of soluble, monomeric gp120-molecules derived from parental HIV-1 Bori and microglia-adapted HIV-1 Bori-15 was assessed in ELISA binding assays using FI05, IgG1b12, 17b and 48d, 2G12 and 447-52D. Association rates of sCD4 and 17b were not changed, but dissociation rates were 3-fold slower for sCD4 and 14-fold slower for 17b. Equilibrium binding studies showed 48d bound better to Bori-15 than Bori in the absence of sCD4, while 17b bound identically. Martín-García *et al.* [2005] (**antibody binding site definition and exposure**)
- 48d: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened while not obscuring b12 binding. CD4i MAbs (48d, 17b) did not bind to either GDMR or mCHO even with sCD4. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
- 48d: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 48d: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) and two sites adjacent to V3, C2 (GM292 C2) and (GM329 C3), increased neutralization susceptibility to CD4i Fab X5, but each of the glycan mutants and SF162 were refractive to neutralization with 48d and 17b. The loss of sites in C4 (GM438



- C4), or V5 (GM454 V5) did not increase neutralization susceptibility to Fab X5. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure, vaccine antigen design**)
- 48d: A set of HIV-1 chimeras that altered V3 net charge and glycosylation patterns in V1V2 and V3, involving inserting V1V2 loops from a late stage primary isolate taken after the R5 to X4 switch, were studied with regard to phenotype, co-receptor usage, and MAb neutralization. The loops were cloned into a HXB2 envelope with a LAI viral backbone. It was observed that the addition of the late-stage isolate V1V2 region and the loss of V3-linked glycosylation site in the context of high positive charge gave an X4 phenotype. R5X4, R5, and X4 viruses were generated, and sCD4, 2G12 and b12 neutralization resistance patterns were modified by addition of the late stage V1V2, glycosylation changes, and charge in concert, while neutralization by 2F5 was unaffected. 15e, 17b, and 48d could not neutralize any of the variants tested. Nabatov *et al.* [2004] (**antibody binding site definition and exposure, co-receptor**)
  - 48d: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 48d. Pantophlet *et al.* [2004] (**vaccine antigen design**)
  - 48d: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three CD4i MAbs were tested; all preferentially neutralized SF162, and JRFL became neutralization sensitive to CD4i Abs if the SF162 V1V2 loop was exchanged. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
  - 48d: Called 4.8d. The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. B4e8 enhanced binding of CD4i MAbs 4.8d, 1.7b, and A1g8 to R5X4 virus 92HT593, but only of 48d to the R5 virus 92US660, and there was only a modest impact of the combination of B4e8 and CD4i MAbs on neutralization. Cavacini *et al.* [2003] (**antibody interactions, co-receptor**)
  - 48d: 48d was used as a negative control to test CDR3 tyrosine sulfation of MAbs 47e, 412d, CM51 and E51, since it lacks CDR3 tyrosines. As expected, 48d did not incorporate sulfates while the other MAbs did. Neutralization assays showed that 48d was less efficient at neutralizing primary R5 and R5X4 isolates than MAbs 412d and E51, however, it was more efficient at neutralizing X4 isolates than these MAbs. Choe *et al.* [2003] (**antibody binding site definition and exposure, neutralization**)
  - 48d: This study shows the fragments of CD4i MAbs are better able to neutralize virus than whole IgG. Neutralization of HIV-1 R5 isolates JRFL, JR-CSF and ADA by CD4i MAbs X5, 17b, and 48d decreased with increased molecule size, the neutralizing potency of single-chain Fv (scFv) > than Fab fragments > whole Ab molecules. (With the exception of IgG 48d neutralization of HIV-1 ADA being better than the Fab – for 48d, only the IgG and Fab forms were available, not the scFv.) HIV-1 X4 isolates 89.6 and HxB2 are both relatively sensitive even to the larger IgG version. R5X4 isolate neutralization was dependent on the isolate and co-receptor usage. The CD4i MAb fragments neutralize HIV-1 subsequent to CD4 binding. The CD4i MAbs bind near the co-receptor binding sites on gp120. Co-receptors bind to the conserved beta19 strand and part of the V3 loop, regions that are masked by the V1V2 loops in the CD4-unbound state. When CD4 is bound, the co-receptor site is exposed near the membrane surface where it would be optimally accessible to co-receptors, and the smaller versions of the molecules are better able to overcome the steric hindrance. Labrijn *et al.* [2003] (**antibody binding site definition and exposure, co-receptor, variant cross-recognition or cross-neutralization**)
  - 48d: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
  - 48d: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a CD4i MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
  - 48d: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-V3 MAb B4a1 increased binding of CD4i MAbs 48d, 17b and A1g8, but only A1g8 binding was increased by B4a1 to the R5 isolate. Additive effects on neutralization of the R5X4 isolate with B4a1 and CD4i MAbs was observed, presumably due to increased exposure of the CD4i binding site, but not for the R5 isolate. Anti-gp41 MAb F240 had a synergistic effect on neutralization with CD4i MAbs 48d and 17b, but not with A1g8 for the R5X4 virus. Cavacini *et al.* [2002] (**variant cross-recognition or cross-neutralization**)

- 48d: Truncation of the gp41 cytoplasmic domain of X4, R5, and X4R5 viruses forces a conformation that more closely resembles the CD4 bound state of the external Envelope, enhancing binding of CD4i MAbs 17b and 48d and of CD4BS MAbs F105, b12, and in most cases of glycosylation site dependent MAb 2G12 and the anti-gp41 MAb 246D – in contrast, binding of the anti-V2 MAb 697D and the anti-V3 MAb 694/98D were not affected – viruses bearing the truncation were more sensitive to neutralization by MAbs 48d, b12, and 2G12 – the anti-C5 MAb 1331A was used to track levels of cell surface expression of the mutated proteins. Edwards *et al.* [2002] (**co-receptor**)
- 48d: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – the preincubation 31.5 C step did not alter the inhibitory activity of neutralizing Abs anti-gp41 2F5, or anti-gp120 2G12, IG1b12, 48d, and 17b. Golding *et al.* [2002b]
- 48d: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar. Enthalpy and entropy changes were divergent, but compensated. Not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs (17b, 48d, 1.5e, b6, F105 and F91) had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, but the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. The high values suggest surface burial or protein folding an ordering of amino acids. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- 48d: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b]
- 48d: Five CD4i MAbs were studied, 17b, 48d and three new MAbs derived by Epstein-Barr virus transformation of PBMC from an HIV+ long term non-progressor – 23e and 21c were converted to hybridomas to increase Ab production – all compete with the well-characterized 17b CD4i MAb in an ELISA antigen capture assay – critical binding residues are mapped and the CD4i MAb epitopes were distinct but share a common element near isoleucine 420, also important for CCR5 binding, and all five can block CCR5 binding to a sCD4-gp120 complex – the MAb 48d has the epitope most similar to the CCR5 binding site. Xiang *et al.* [2002a] (**antibody binding site definition and exposure, co-receptor**)
- 48d: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibrin – stabilized oligomer gp140 delta683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002]
- 48d: Called 4.8D – A rare mutation in the neutralization sensitive R2-strain in the proximal limb of the V3 region caused Env to become sensitive to neutralization by MAbs directed against the CD4 binding site (CD4BS), CD4-induced (CD4i) epitopes, soluble CD4 (sCD4), and HNS2, a broadly neutralizing sera – 2/12 anti-V3 MAbs tested (19b and 694/98-D) neutralized R2, as did 2/3 anti-CD4BS MAbs (15e and IgG1b12), 2/2 CD4i MAbs (17b and 4.8D), and 2G12 and 2F5 – thus multiple epitopes on R2 are functional targets for neutralization and the neutralization sensitivity profile of R2 is intermediate between the highly sensitive MN-TCLA strain and the typically resistant MN-primary strain. Zhang *et al.* [2002] (**variant cross-recognition or cross-neutralization**)
- 48d: Using a cell-fusion system, it was found CD4i antibodies 17b, 48d, and CG10 reacted faintly with Env expressing HeLA cells even in the absence of sCD4 or CD4 expressing target cells. Reactivity increased after sCD4 addition, but not after CD4 expressing target cell addition, and binding was not increased at the cell-to-cell CD4-Env interface. This suggests the CD4i co-receptor binding domain is largely blocked at the cell-fusion interface, and so CD4i antibodies would not be able access this site and neutralize cell-mediated viral entry. Finnegan *et al.* [2001] (**antibody binding site definition and exposure**)
- 48d: Mutations in two glycosylation sites in the V2 region of HIV-1 ADA at positions 190 and 197 (187 DNTSYRLINCNNTS 199) cause the virus to become CD4-independent and able to enter cells through CCR5 alone – these same mutations tended to increase the neutralization sensitivity of the virus, including to 48d – only the CD4i antibodies 17b and 48d showed an increased affinity of the CD4 independent viruses relative to wild-type. Kolchinsky *et al.* [2001]
- 48d: Called 4.8d – A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001]

- 48d: Called 4.8D – host encoded intercellular adhesion molecule (ICAM-1) is incorporated by the HIV-1 virion and enhances viral infectivity – ICAM-1 does not modify virus sensitivity to antibodies 0.5beta or 4.8D or sCD4, but neutralizing ability of F105 was diminished in ICAM bearing virions in the presence of lymphocyte function-association antigen-1 (LFA-1) Ab. Fortin *et al.* [2000]
- 48d: SF162 is a neutralization-resistant HIV-1 isolate – N-linked glycosylation modifications in the V2 loop of the SF162 gp120 revealed that these sites prevent neutralization by CD4BS MAbs (IgG1b12 and IgGCD4), and protect against neutralization by V3 MAbs (447-D and 391-95D) – V2-region glycosylation site mutations did not alter neutralization resistance to V2 MAbs (G3.4 and G3.136) or CD4i MAbs (17b and 48d) – V2 glycosylation site modification allows infection of macrophages, probably due to glycosylated forms requiring fewer CCR5 molecules for viral entry. Ly & Stamatatos [2000]
- 48d: Six mutations in MN change the virus from a high-infectivity neutralization resistant phenotype to low-infectivity neutralization sensitive – V3, CD4BS, and CD4i MAbs are 20-100 fold more efficient at neutralizing the sensitive form – the mutation L544P reduced binding of all MAbs against gp120 by causing conformational changes. Park *et al.* [2000]
- 48d: sCD4 can activate fusion between effector cells expressing Env and target cells expressing coreceptor (CCR5 or CXCR4) alone without CD4 – CD4i MAbs 17b and 48d have little effect on a standard cell fusion assay but potently block sCD4 activated fusion. Salzwedel *et al.* [2000] (**co-receptor**)
- 48d: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) that preserve and expose some neutralizing epitopes while occluding some non-neutralizing epitopes – CD4BS MAbs (F105 and F91) and CD4i (17b and 48d) recognized gp140-GNC4 as well as gp120 or gp140 – non-neutralizing MAbs C11, A32, 522-149, M90, and #45 bound to the gp140-GNC4 glycoprotein at reduced levels compared to gp120 – MAbs directed at the extreme termini of gp120 C1 (135/9 and 133/290) and C5 (CRA-1 and M91) bound efficiently to gp140-GNC4. Yang *et al.* [2000]
- 48d: A CD4-independent viral variant of IIIB, IIIBx, was generated on CXCR4-expressing cells – IIIBx exhibited greater exposure of the 17b and 48d epitopes and enhanced neutralization by CD4i MAbs and by polyclonal human sera. Hoffman *et al.* [1999]
- 48d: A panel of MAbs were shown to bind with similar or greater affinity and similar competition profiles to a deglycosylated or variable loop deleted core gp120 protein (Delta V1, V2, and V3), thus such a core protein produces a structure closely approximating full length folded monomer – CD4i MAbs 17b and 48d bound better to the deleted protein than to wild type. Binley *et al.* [1998]
- 48d: Infection of dendritic cells cultured from CD14+ blood cells or from cadaveric human skin was blocked by neutralizing MAbs IgG1b12, or 2F5 and 2G12 delivered together, but not by control non-neutralizing anti-gp120 MAb 4.8D, indicating that NABs could interrupt early mucosal transmission events. Frankel *et al.* [1998]
- 48d: Inhibits binding of Hx10 to both CD4 positive and CD4 negative HeLa cells. Mondor *et al.* [1998]
- 48d: The MAb and Fab binding to the oligomeric form of gp120 and neutralization were highly correlated – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a]
- 48d: Deleting the V2 loop of neutralization-resistant HIV-1 isolate SF162 does not abrogate its replication in PBMC or macrophages, but it enhances its neutralization sensitivity to sera from patients with B clade infection up to 170-fold, and also enhances sensitivity to sera from clades A through F – deletion of V2 but not V1 enabled neutralization by CD4i MAbs 17b and 48d. Stamatatos & Cheng-Mayer [1998]
- 48d: CD4i MAbs 17b and 48d compete with MAb CG10, and the binding sites may overlap – MAb A32 enhances binding of 17b, 48d and CG10. Sullivan *et al.* [1998b]
- 48d: Summary of the implications of the crystal structure of the core of gp120 bound to CD4 and 17b with what is known about mutations that reduce NAB binding – probable mechanism of neutralization of 48d is interference with chemokine receptor binding – CD4 binding increases exposure of epitope due to V2 loop movement – 88N, 117K, 121K, 256S, 257T, N262, delta V3, E370, E381, F 382, R 419, I 420, K 421, Q 422, I 423, W 427, Y 435, P 438, M 475 mutations in HXBc2 (IIIB) decrease binding. Wyatt *et al.* [1998] (**structure**)
- 48d: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998]
- 48d: Prefers CD4-gp120 complex to gp120 alone, but does not enhance fusion, in contrast to MAb CG10, in fact it inhibits syncytium formation. Lee *et al.* [1997] (**antibody binding site definition and exposure**)
- 48d: One of 14 human MAbs tested for ability to neutralize a chimeric SHIV-vpu+, which expressed HIV-1 IIIB env – all Ab combinations tested showed synergistic neutralization – 48d has synergistic response with MAbs 694/98-D (anti-V3) and F105. Li *et al.* [1997] (**antibody interactions**)
- 48d: Neutralizes TCLA strains, but not primary isolates. Parren *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)
- 48d: Viral binding inhibition by 48d was strongly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5). Ugolini *et al.* [1997]
- 48d: 48d binds to the IIIB protein and not IIIB V3 peptide, while binding to the Can0A V3 peptide, suggesting Can0A V3 is a conformer that mimics the 48d, (but not 17b), epitope. Weinberg *et al.* [1997] (**antibody binding site definition and exposure**)
- 48d: Binds efficiently to sgp120 but not soluble gp120+gp41, suggesting its gp120 epitope is blocked by gp41 binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- 48d: Many MAbs inhibit binding (anti-C1, -C5, -C4, -CD4BS) – anti-C1-C4 discontinuous epitope MAbs A32 and

2/11c enhance binding – reciprocal enhanced binding with some anti-V2 MAbs. Moore & Sodroski [1996] (**antibody interactions**)

- 48d: Binding resulted in gp120 dissociation from virion, mimicking sCD4, and exposure of the gp41 epitope of MAb 50-69, in contrast to CD4BS MAbs. Poignard *et al.* [1996a] (**antibody interactions**)
- 48d: Neutralizes JR-FL – slightly inhibits gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study. Trkola *et al.* [1996a] (**antibody binding site definition and exposure, co-receptor**)
- 48d: Called 4.8D – Found to neutralize MN, but not JRCSF, two B subtype primary isolates, or a D subtype primary isolate, by most labs in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- 48d: Formalin inactivation of virus at 0.1% formalin for 10 hours at 4 degrees was optimal for inactivation of virus while maintaining epitope integrity. Sattentau *et al.* [1995] (**vaccine antigen design**)
- 48d: Binds with similar affinity to monomer and oligomer, moderate association rate, potent neutralization – this is in contrast to 17b, which has very different kinetics. Sattentau & Moore [1995] (**antibody binding site definition and exposure, kinetics, binding affinity**)
- 48d: Studies using a V1/V2 deletion mutant demonstrated that enhanced binding of 48d in the presence of sCD4 involves the V1/V2 loops, with more significant involvement of V2 – similar effect observed for 17b and A32. Wyatt *et al.* [1995] (**vaccine antigen design**)
- 48d: Poor cross-reactivity with gp120 from most clades. Moore *et al.* [1994b] (**subtype comparisons**)
- 48d: A mutation in gp41, 582 A/T, confers resistance to neutralization (also confers resistance to MAbs F105, 21h, 15e and 17b). Thali *et al.* [1994] (**variant cross-recognition or cross-neutralization**)
- 48d: Called 4.8d – Neutralizes IIIB – reactive with SF-2 gp120 – does not inhibit HIV-1 sera from binding to IIIB gp120. Moore & Ho [1993] (**variant cross-recognition or cross-neutralization**)
- 48d: Binding of 48d is much more influenced by sequence variation among molecular clones of LAI than is binding of 17b. Moore *et al.* [1993c] (**variant cross-recognition or cross-neutralization**)
- 48d: Epitope is better exposed upon CD4 binding to gp120 – competes with ICR 39.13, 15e and 21h, anti-CD4 binding site MAbs – inhibited by anti-CD4BS MAb ICR 39.13g and linear anti-C4 MAbs G3-42 and G3-508 – 113 D/R, 252 R/W, 257 T/A or G, 370 E/D, 382 F/L, 420 I/R, 421 K/L, 433A/L, 438 P/R and 475 M/S confer decreased sensitivity to neutralization. Thali *et al.* [1993] (**antibody binding site definition and exposure, antibody interactions**)

No. 1227

MAb ID 49e

HXB2 Location Env

Author Location gp120 (IIIB, J62)

Epitope

Subtype B

Neutralizing L

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4i

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**References** Gorny & Zolla-Pazner 2004; Xiang *et al.* 2002b; Xiang *et al.* 2002a

**Keywords** antibody binding site definition and exposure, antibody generation, review, vaccine antigen design

- 49e: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 49e: Five CD4i MAbs were studied, 17b, 48d and three new MAbs derived by Epstein-Barr virus transformation of PBMC from an HIV+ long term non-progressor – 23e and 21c were converted to hybridomas to increase Ab production – all compete with the well-characterized 17b CD4i MAb in an ELISA antigen capture assay – critical binding residues are mapped and the CD4i MAb epitopes were distinct but share a common element near isoleucine 420, also important for CCR5 binding, and all five can block CCR5 binding to a sCD4-gp120 complex – the MAb 48d has the epitope most similar to the CCR5 binding site. Xiang *et al.* [2002a] (**antibody binding site definition and exposure, antibody generation**)
- 49e: A series of mutational changes were introduced into the YU2 gp120 that favored different conformations – 375 S/W seems to favor a conformation of gp120 closer to the CD4-bound state, and is readily bound by sCD4 and CD4i MAbs (17b, 48d, 49e, 21c and 23e) but binding of anti-CD4BS MAbs (F105, 15e, IgG1b12, 21h and F91) was markedly reduced – IgG1b12 failed to neutralize this mutant, while neutralization by 2G12 was enhanced – 2F5 did not neutralize either WT or mutant, probably due to polymorphism in the YU2 epitope – another mutant, 423 I/P, disrupted the gp120 bridging sheet, favored a different conformation and did not bind CD4, CCR5, or CD4i antibodies, but did bind to CD4BS MAbs. Xiang *et al.* [2002b] (**antibody binding site definition and exposure, vaccine antigen design**)

No. 1228

MAb ID Fbb21

HXB2 Location Env

Author Location gp120

Epitope

Neutralizing

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 CD4i

**References** Zwick *et al.* 2003

**Keywords** antibody interactions

- Fbb21: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact

4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4i Fab first used in this study. Fbb21, like other CD4i MAbs, did not inhibit or enhance 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)

**No.** 1229  
**MAB ID** Fbb21  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 CD4i  
**References** Zwick *et al.* 2003  
**Keywords** antibody interactions

- Fbb21: scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This is a novel CD4i Fab first used in this study. Fbb21, like other CD4i MAbs, did not inhibit or enhance 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)

**No.** 1230  
**MAB ID** X5 (Fab X5)  
**HXB2 Location** Env  
**Author Location** gp120 (JRFL)  
**Epitope**  
**Subtype** B  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 CD4i  
**References** Cham *et al.* 2006; Choudhry *et al.* 2006; Bowley *et al.* 2007; Pinter *et al.* 2004; Pantophlet *et al.* 2004; McCaffrey *et al.* 2004; Darbha *et al.* 2004; Binley *et al.* 2004; Gorny & Zolla-Pazner 2004; Pantophlet *et al.* 2003b; Zwick *et al.* 2004; Zwick *et al.* 2003; Zhang *et al.* 2003; Labrijn *et al.* 2003; Binley *et al.* 2003; Moulard *et al.* 2002  
**Keywords** antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay standardization/improvement, binding affinity, co-receptor, neutralization, review, structure, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- X5: A direct comparison of phage and yeast display libraries was undertaken, and yeast display sampled the immune repertoire more fully. Previous results from panning a phage library generated from a long-term non-progressor were compared directly with a yeast library. As determined by sequencing, many MAbs were common to both, although the yeast library identifies unique scFv. X5 was identified using both methods. Bowley *et al.* [2007] (**antibody generation, binding affinity, antibody sequence variable domain, assay standardization/improvement**)
- X5: Cloned Envs (clades A, B, C, D, F1, CRF01\_AE, CRF02\_AG, CRF06\_cpx and CRF11\_cpx) derived from donors either with or without broadly cross-reactive neutralizing antibodies were shown to be of comparable susceptibility to neutralization by X5. Cham *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- X5: Neutralization of HIV-1 primary isolates from different clades (B, C, D and E) by X5 was determined in cells expressing high or low surface concentrations of CD4 and CCR5 receptors. CD4 cell surface concentration had no effect on the inhibitory activity of this Ab while the CCR5 surface concentration had a significant effect decreasing the 50% inhibitory concentration of X5 in cell lines with low CCR5. Choudhry *et al.* [2006] (**co-receptor, neutralization, variant cross-recognition or cross-neutralization, subtype comparisons**)
- X5: 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV antibodies. X5 is a CD4i antibody and neutralized only the most sensitive B-clade envelopes in the pseudovirus assay, but was able to neutralize 2/25 non-B isolates in the PBMC assay, possibly due to differential coreceptor expression. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- X5: The structure of the Fab X5 was determined at 1.9 angstrom resolution. The binding site is a long, 22 amino acid CDR H3 with a hook shape. Long CDR H3s are also found in IgG1b12 (18 residues) and 17b (19 residues). Fab X5 has a W100, F100Y in the CDR H3 hook shown to be important for binding through site specific mutagenesis. Compared to JRCSF, Ala substitutions at eight residues reduced binding more than 3 fold: C119, K207, G367, M426, W427, V430, I423, and K432. Only I423A and K432A were thought to possibly directly interact with X5, the other mutations were thought likely to disrupt the overall structure or CD4 binding. Darbha *et al.* [2004] (**antibody binding site definition and exposure, structure**)
- X5: This review summarizes MAbs directed to HIV-1 Env. There are six CD4 inducible MAbs and Fabs in the database. The MAb forms neutralize TCLA strains only, but the smaller Fabs and scFv fragments can neutralize primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- X5: Sera from two HIV+ people and a panel of MAbs were used to explore susceptibility to neutralization in the presence or absence of glycans within or adjacent to the V3 loop and within the C2, C4 and V5 regions of HIV-1 SF162 env gp120. The loss of the glycan within the V3 loop (GM299 V3) and two sites adjacent to V3, C2 (GM292 C2) and (GM329 C3),

increased neutralization susceptibility to CD4i FAb X5, but each of the glycan mutants and SF162 were refractive to neutralization with 48d and 17b. The loss of sites in C4 (GM438 C4), or V5 (GM454 V5) did not increase neutralization susceptibility to FAb X5. V3 glycans tended to shield V3 loop, CD4 and co-receptor MAb binding sites, while C4 and V5 glycans shielded V3 loop, CD4, gp41 but not co-receptor MAb binding sites. Selective removal of glycans from a vaccine candidate may enable greater access to neutralization susceptible epitopes. McCaffrey *et al.* [2004] (**antibody binding site definition and exposure, vaccine antigen design**)

- X5: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including X5. Pantophlet *et al.* [2004] (**vaccine antigen design**)
- X5: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three CD4i MAbs were tested; all preferentially neutralized SF162, and JRFL became neutralization sensitive to CD4i Abs if the SF162 V1V2 loop was exchanged. FAb X5 could neutralize both viruses, but had reduced potency against JRFL. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- X5: Called Fab X5. This paper is a study of the 2F5 NAb complexed to peptide ELDKWAS; the peptide was found to interact with amino acids near the base of the very long (22 residue) CDR 3H region of the Ab, although a Phe at the apex of the loop was also important. The authors suggest that particularly long CDR H3 regions may be a common feature of HIV-1 neutralizing antibodies – there are 22 residues in 2F5's H3, 18 in b12's H3, and 22 residues in X5's H3. They express concern that because small animals like mice are unable to elicit Ab responses with such long H3s, they may be poor model systems for HIV vaccine studies. Zwick *et al.* [2004] (**antibody interactions**)
- X5: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. CD4i Abs X5 and 17b were weakly neutralizing in all formats, WT, SOS, and when added postbinding. Binley *et al.* [2003] (**vaccine antigen design**)
- X5: This study shows the fragments of CD4i MAbs are better able to neutralize virus than whole IgG. Neutralization of HIV-1 R5 isolates JRFL, JR-CSF and ADA by CD4i MAbs X5, 17b, and 48d decreased with increased molecule size, the neutralizing potency of single-chain Fv (scFv) > than Fab fragments > whole Ab molecules. (With the exception of IgG 48d neutralization of HIV-1 ADA.) HIV-1 X4 isolates 89.6 and HxB2 are both relatively sensitive even to the larger IgG version. R5X4 isolate neutralization was dependent on the isolate and co-receptor usage. The CD4i MAb fragments neutralize HIV-1 subsequent to CD4 binding. The CD4i MAbs bind near the co-receptor binding sites on gp120. Co-receptors bind to the conserved beta19 strand and part of the V3 loop, regions that are masked by the V1V2 loops in the CD4-unbound state. When CD4 is bound, the co-receptor site is exposed near the membrane surface where it would be optimally accessible to co-receptors, and the smaller versions of the molecules are better able to overcome the steric hindrance. Labrijn *et al.* [2003] (**antibody binding site definition and exposure, co-receptor, variant cross-recognition or cross-neutralization**)
- X5: A gp120 molecule was designed to focus the immune response onto the IgG1b12 epitope. Ala substitutions that enhance the binding of IgG1b12 and reduce the binding of non-neutralizing MAbs were combined with additional N-linked glycosylation site sequons inhibiting binding of non-neutralizing MAbs; b12 bound to the mutated gp120. C1 and C5 were also removed, but this compromised b12 binding. Pantophlet *et al.* [2003b] (**vaccine antigen design**)
- X5: The Fab m18 was selected from a human phage display library by a new method called sequential antigen panning (SAP), using a series of antigens to screen the library to pick broadly cross-reactive isolates. The ability to block cell mediated fusion by m18 was compared to Fabs X5 and b12 for a clade A, CRF01 EA, G, and 6 clade B isolates, and the inhibitory activity of m18 was slightly lower but comparable to neutralizing Fabs b12 and X5. It also showed broad cross-neutralization; 11/15 pseudotyped Envs from primary isolates from clades A-F were inhibited in an IC50 assay at concentration less than or equal to 100 ug/ml; X5 was also tested and somewhat more potent, generally requiring lower concentrations and inhibiting 13/15 primary isolates. Zhang *et al.* [2003] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- X5: scFv 4KG5 reacts with a conformational epitope. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120. MAbs to the V2 loop, V3 loop, V3-C4 region, and CD4BS diminished binding, while MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected. This is a CD4i MAb that had no impact on 4KG5 binding. Zwick *et al.* [2003] (**antibody interactions**)
- X5: The human Fab X5 was selected from a phage display library derived from an HIV-1 positive donor with a highly neutralizing serum – it was selected for binding to purified gp120-CD4-coreceptor complexes – the Fab neutralizes PBMC infection by a selection of HIV-1 primary isolates from clades A, B,

C, D, E, F, and G, and neutralizes R5, X4, and R5X4 isolates – it binds to a conserved epitope on gp120 induced by CD4 binding, its binding is slightly enhanced by CCR5 binding – while CD4i MAb 17b binds the CCR5 binding site, X5 also competes with Fab b12 which overlaps with the CD4 binding site, suggesting the epitope for is near both the CD4 and CCR5 binding sites. Moulard *et al.* [2002] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 1231

**MAb ID** 8F101

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* sCD4-gp120 complex *Strain:* B clade HXB2 *HIV component:* gp120

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 CD4i, gp120-CD4 complex

**Research Contact** Ranajit Pal, Advanced BioScience Lab, Inc.

**References** Finnegan *et al.* 2002; Finnegan *et al.* 2001; DeVico *et al.* 1995

**Keywords** antibody binding site definition and exposure, antibody generation, kinetics

- 8F101: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I and Cluster II MAbs required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor, binding to a fusion intermediate. 8F101 selectively stains gp120-CD4 complexes after dissociation from gp41, and did not stain cells arrested earlier than 30 min of co-culture, but 8F101 and cluster I and II MAbs co-localized at fusing cell interfaces at 30 min coculture. After extended co-culture, only 8F101 bound. Finnegan *et al.* [2002] (**antibody binding site definition and exposure, kinetics**)
- 8F101: Using a cell-fusion system, it was found CD4i antibodies 17b, 48d, and CG10 reacted faintly with Env expressing HeLa cells even in the absence of sCD4 or CD4 expressing target cells. Reactivity increased after sCD4 addition, but not after CD4 expressing target cell addition, and binding was not increased at the cell-to-cell CD4-Env interface. This suggests the CD4i co-receptor binding domain is largely blocked at the cell-fusion interface, and so CD4i antibodies would not be able access this site and neutralize cell-mediated viral entry. However, CD4i MAbs 8F101 and A32, that bind outside the co-receptor domain, had a different pattern. They reacted after the formation of gp120-CD4-CXCR4 tri-complexes, so co-receptor interactions allowed exposure of their epitopes. Finnegan *et al.* [2001] (**antibody binding site definition and exposure**)
- 8F101: MAbs specifically reactive to crosslinked gp120 and CD4 were derived (8F101, 8F102) – conformation dependent – competition studies indicate the epitope is immunogenic in infected humans. DeVico *et al.* [1995] (**antibody generation**)

**No.** 1232

**MAb ID** T22

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** Env oligomer

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Otteken *et al.* 1996; Earl *et al.* 1994

- T22: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T22 is part of a group of MAbs labeled AII – all AII MAbs were broadly cross-reactive with gp160 from B-clade R5, X4, and R5X4 viruses, and could only partially blocked CD4 binding. Sugiura *et al.* [1999]
- T22: Pulse label experiments of 4 MAbs (D20, D27, T20, and T22) binding to noncleavable gp140 revealed that these anti-CD4BS MAbs bound with a delay, and that the epitope formed with a t 1/2 of about 10 minutes. Otteken *et al.* [1996]
- T22: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1233

**MAb ID** 2A2

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** N-term

**References** Weissenhorn *et al.* 1996

- Soluble gp41(21-166) forms a rod like structure that can be visualized with electron microscopy, and 2A2 binds to one end of the rod. Weissenhorn *et al.* [1996]

**No.** 1234

**MAb ID** AC4

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* gp160

**Species (Isotype)** mouse

**Ab Type** N-term

**References** Dickey *et al.* 2000

- AC4: Three MAbs, ID6, AC4, and AD3 that bind to a discontinuous N-term first 204 aa of gp120 and generate ADCC were elicited through vaccination of BALBc mice with rec gp160 – these MAbs do not depend on glycosylation and are cross-reactive with viruses from clades B and CRF01(AE). Dickey *et al.* [2000]

**No.** 1235  
**MAb ID** AD3  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp160  
**Species (Isotype)** mouse  
**Ab Type** N-term  
**References** Cook *et al.* 1994; Dickey *et al.* 2000

- AD3: There may be two Abs with this name that bind to the N-term region of gp120. Cook *et al.* [1994]; Dickey *et al.* [2000]
- AD3: Three MABs, ID6, AC4, and AD3 that bind to a discontinuous N-term first 204 aa of gp120 and generate ADCC were elicited through vaccination of BALBc mice with rec gp160 – these MABs do not depend on glycosylation and are cross-reactive with viruses from clades B and CRF01(AE). Dickey *et al.* [2000]

**No.** 1236  
**MAb ID** AD3  
**HXB2 Location** Env  
**Author Location** gp120 (BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** N-term  
**References** Dickey *et al.* 2000; Cook *et al.* 1994; Ugen *et al.* 1993

- AD3: NIH AIDS Research and Reference Reagent Program: 2342.
- AD3: There may be two Abs with this name that bind to the N-term region of gp120. Cook *et al.* [1994]; Dickey *et al.* [2000]
- AD3: MABs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MABs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]

**No.** 1237  
**MAb ID** ID6  
**HXB2 Location** Env  
**Author Location** gp120 (1–193 BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** N-term  
**References** Dickey *et al.* 2000; Cook *et al.* 1994; Ugen *et al.* 1993

- ID6: NIH AIDS Research and Reference Reagent Program: 2343.
- ID6: There may be two Abs with this name that bind to the N-term region of gp120. Cook *et al.* [1994]; Dickey *et al.* [2000]

- ID6: MABs against the glycosphingolipid GalCer block HIV infection of normally susceptible CD4 negative cells from the brain and colon – MABs against the N-terminal half of gp120 do not inhibit gp120 binding to GalCer – binding of GalCer to gp120 does not inhibit MAb binding. Cook *et al.* [1994]

**No.** 1238  
**MAb ID** ID6  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp160  
**Species (Isotype)** mouse (IgG2a)  
**Ab Type** N-term  
**References** Cook *et al.* 1994; Dickey *et al.* 2000

- ID6: There may be two Abs with this name that bind to the N-term region of gp120. Cook *et al.* [1994]; Dickey *et al.* [2000]
- ID6: Three MABs, ID6, AC4, and AD3 that bind to a discontinuous N-term first 204 aa of gp120 and generate ADCC were elicited through vaccination of BALBc mice with rec gp160 – these MABs do not depend on glycosylation and are cross-reactive with viruses from clades B and CRF01(AE). Dickey *et al.* [2000]

**No.** 1239  
**MAb ID** 11/68b  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L (HXB2)  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10 *HIV component:* gp120  
**Species (Isotype)** rat (IgG1)  
**Ab Type** gp120 V1-V2  
**Research Contact** Shotton and Dean  
**References** Holl *et al.* 2006a; Peet *et al.* 1998; Shotton *et al.* 1995; McKeating *et al.* 1993b  
**Keywords** dendritic cells, neutralization

- 11/68b: 435 (Y/H) in C4 does not abrogate binding (John Moore, per comm, 1996).
- 11/68b: UK Medical Research Council AIDS reagent: ARP3041.
- 11/68b: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 11/68b: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MABs to V1/V2, C1 and C4 to bind – 11/68b was not affected by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]



- 11/68b: Cross-competes with MAbs 62c, 66c, 66a, and CRA-4 – similar to MAb 62c – HXB2 neutralization escape mutant had a D/N substitution at residue 185 – non-reciprocal inhibition of binding of CRA-3 and CRA-6. Shotton *et al.* [1995]
- 11/68b: Changes at residues 183/184 (PI/SG) within V2, 435 (Y/H) in C4, abrogate binding. McKeating *et al.* [1993b]

**No.** 1240  
**MAb ID** 62c  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)** rat (IgG1)  
**Ab Type** gp120 V1-V2  
**References** Holl *et al.* 2006a; Shotton *et al.* 1995  
**Keywords** dendritic cells, neutralization

- 62c: UK Medical Research Council AIDS reagent: ARP3075.
- 62c: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 62c: Cross-competes with MAbs 11/68b, 66c, 66a, and CRA-4 – same cross-competition group as MAb 11/68b – non-reciprocal inhibition of binding of CRA-3 and CRA-6 – substitutions 176-177 FY/AT, 179-180 LD/DL, 183-184 PI/SG, and 191-193 YSL/GSS abrogate binding – binds but does not neutralize Hx10. Shotton *et al.* [1995]

**No.** 1241  
**MAb ID** CRA-6 (CRA6)  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)** mouse  
**Ab Type** gp120 V1-V2  
**References** Shotton *et al.* 1995

- CRA-6: Called CRA6 – same competition group as CRA-3. Shotton *et al.* [1995]

**No.** 1242  
**MAb ID** L15  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** P (weak)  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1)  
**Ab Type** gp120 V1-V2  
**References** Gorny & Zolla-Pazner 2004; Parren *et al.* 1997b; Ditzel *et al.* 1997  
**Keywords** review, variant cross-recognition or cross-neutralization

- L15: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weak with limited cross-reactivity. L15 and L17 are Fabs specific for V2. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- L15: gp120 immobilized on solid phase by capture with anti-CD4 BS MAb L72 was used for selection of Fabs – 2 anti-V2 Fabs were obtained with very similar epitopes, L15 and L17 – deletions in V1 and V2 abolished binding, and rodent anti-V2 MAbs SC258, CRA3, G3-G4,G3-136, BAT-085, and 52-684 all compete with L15. Ditzel *et al.* [1997]
- L15: Does not neutralize TCLA strains but neutralizes some primary isolates weakly. Parren *et al.* [1997b]

**No.** 1243  
**MAb ID** T52  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 V1-V2  
**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD  
**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- T52: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T52 is one of two MAbs labeled B-II, that had limited cross-reactivity with seven clade B isolates and did not fully blocked CD4 binding – deletion of V1/V2 loops abrogated binding. Sugiura *et al.* [1999]
- T52: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1244  
**MAb ID** T54  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* vaccinia *Strain:* B clade IIIB  
*HIV component:* oligomeric gp140  
**Species (Isotype)** mouse (IgG)  
**Ab Type** gp120 V1-V2  
**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD  
**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- T54: A comparison of 25 gp120 specific, conformation dependent MAbs was done – T54 is one of two MAbs labeled B-II, that had limited cross-reactivity with seven clade B isolates and did not fully blocked CD4 binding – deletion of V1/V2 loops abrogated binding. Sugiura *et al.* [1999]
- T54: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

**No.** 1245  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Neutralizing** yes  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 V1-V2 and V3-V5  
**References** Gordon & Delwart 2000

- Primary isolates have great differences in susceptibility to neutralization – the variation in V1V2 and V3-V5 was measured by HTA in a set of viruses with a range of neutralization susceptibilities, and greater variability was uncorrelated with resistance to neutralization. Gordon & Delwart [2000]

**No.** 1246  
**MAb ID** 1088  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**  
**Ab Type** gp120 V2  
**References** Berman *et al.* 1997

- 1088: Binds weakly to 2/7 isolates from breakthrough cases from a MN gp120 vaccine trial. Berman *et al.* [1997]

**No.** 1247  
**MAb ID** 110-B  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* HIV infected-cell lysate  
*Strain:* B clade BRU *HIV component:* HIV-1

**Species (Isotype)** mouse  
**Ab Type** gp120 V2  
**Research Contact** Hybridolabs, Institute Pasteur, Paris, France  
**References** Moore *et al.* 1993a

- 110-B: specific for BH10, does not bind to MN, RF, or SF-2 gp120 – binding inhibited by deletion of the V2 loop, and the following amino acid substitutions: 168 K/L, 176/177 FY/AT, 179/180 LD/DL, 183/184 PI/SG, and 192-194 YSL/GSS. Moore *et al.* [1993a]

**No.** 1248  
**MAb ID** 1357  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp120 V2

**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

**References** Gorny & Zolla-Pazner 2004; Ling *et al.* 2002; Nyambi *et al.* 2000; Gorny *et al.* 2000; Nyambi *et al.* 1998

**Keywords** antibody binding site definition and exposure, co-receptor, review

- 1357: This broad review of anti-Envelope MAbs notes that V2 MAbs are generally weakly neutralizing at best, and somewhat strain specific. Anti-V2 MAbs 1357, 1361, 1393 are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 1357: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Of three V2 MAbs, only 830A, not 2158 or 1357 was enhanced by V3 peptide binding. Ling *et al.* [2002] (**antibody binding site definition and exposure, co-receptor**)
- 1357: Blocks binding of MAb 697-D to gp120, and doesn't react with a protein from which V1V2 has been deleted – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V2 MAbs 697-D, 1357 and 1361 favored the monomer by approximately 2 fold. Gorny *et al.* [2000]
- 1357: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000]
- 1357: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000]
- 1357: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – V2 Abs 697-D, 1361, and 1357 tended to bind very weakly with a similar pattern of specificity to virions, but bound well to soluble gp120: weak binding only to subtype D MAL. Nyambi *et al.* [1998]

**No.** 1249  
**MAb ID** 1361  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* gp120

**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp120 V2

**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

**References** Nyambi *et al.* 2000; Gorny *et al.* 2000; Nyambi *et al.* 1998

- 1361: Blocks binding of MAb 697-D to gp120, and doesn't react with a protein from which V1V2 has been deleted – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, though anti-V3 and CD4BS MAbs reacted better with the oligomer and V2 and C5 tended to favor the monomer – V2 MAbs 697-D, 1357 and 1361 favored the monomer by approximately 2 fold. Gorny *et al.* [2000]
- 1361: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000]
- 1361: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – V2 Abs 697-D, 1361, and 1357 tended to bind weakly with a similar pattern of specificity to virions, but bound well to soluble gp120: weak binding to 1/4 B clade viruses (CA5), and also weak binding to a subtype D virus, MAL. Nyambi *et al.* [1998]

**No.** 1250

**MAb ID** 1393A

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)**

**Ab Type** gp120 V2

**References** Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000

**Keywords** review, subtype comparisons

- 1393A: This broad review of anti-Envelope MAbs notes that V2 MAbs are generally weakly neutralizing at best, and somewhat strain specific. Anti-V2 MAbs 1357, 1361, 1393A are non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 1393A: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000] (**subtype comparisons**)

**No.** 1251

**MAb ID** 2158

**HXB2 Location** Env

**Author Location** gp120 (LAI)

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen**

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 V2

**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

**References** Pinter *et al.* 2004; Ling *et al.* 2004; Ling *et al.* 2002

**Keywords** antibody binding site definition and exposure, co-receptor, variant cross-recognition or cross-neutralization

- 2158: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. V2 MAbs 830A and 2158 were decreased by trypsin, unaffected by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 2158: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-V2 MAb were tested – both 2158 and 830A bound more strongly to JRFL, but neutralized SF162, and not neutralize JRFL. Thus V2 domains are better neutralization targets in SF162. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 2158: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Of three V2 MAbs, only 830A, not 2158 or 1357 was enhanced by V3 peptide binding. Ling *et al.* [2002] (**antibody binding site definition and exposure, co-receptor**)

**No.** 1252

**MAb ID** 66a

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L (HXB2)

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BH10

*HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 V2

**References** Shotton *et al.* 1995

- 66a: UK Medical Research Council AIDS reagent: ARP3074.
- 66a: Substitutions 176-177 FY/AT, 179-180 LD/DL, 183-184 PI/SG, and 191-193 YSL/GSS abrogate binding – same competition group as CRA4. Shotton *et al.* [1995]

**No.** 1253

**MAb ID** 66c

**HXB2 Location** Env

**Author Location** gp120**Epitope****Neutralizing** L (HXB2)**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade BH10*HIV component:* gp120**Species (Isotype)** mouse (IgG1)**Ab Type** gp120 V2**References** Shotton *et al.* 1995

- 66c: Substitutions 176-177 FY/AT, 179-180 LD/DL, 183-184 PI/SG, and 191-193 YSL/GSS abrogate binding – same competition group as CRA4. Shotton *et al.* [1995]

**No.** 1254**MAb ID** 684-238 (52-684-238, 52-684)**HXB2 Location** Env**Author Location** gp120**Epitope****Neutralizing** L**Immunogen** vaccine*Vector/Type:* protein *Strain:* B clade IIIB*HIV component:* gp120**Species (Isotype)** mouse**Ab Type** gp120 V2**Research Contact** Gerry Robey, Abbott Laboratories**References** Ditzel *et al.* 1997; Moore & Sodroski 1996; Ditzel *et al.* 1995; Gorny *et al.* 1994; Thali *et al.* 1993; Moore *et al.* 1993a

- 684-238: Limited reciprocal enhancement of binding with anti-V3 and C4 region antibodies – reciprocal inhibition with V2 region antibodies. Moore & Sodroski [1996]
- 684-238: Does not compete with IgG1b12, reciprocal inhibition with MAbs L39, L40, and L78. Ditzel *et al.* [1995]
- 684-238: Weakly neutralizing, IC 50 = 84 mug/ml. Gorny *et al.* [1994]
- 684-238: Specific for BH10 or HXB2, does not bind to MN, RF, or SF-2 gp120 – neutralizes BH10 – binding inhibited by deletion of the V2 loop, and the following amino acid substitutions: 176/177FY/AT, 179/180LD/DL, 183/184PI/SG, and 192-194YSL/GSS. Moore *et al.* [1993a]

**No.** 1255**MAb ID** 830A**HXB2 Location** Env**Author Location** gp120**Epitope****Neutralizing****Immunogen** HIV-1 infection**Species (Isotype)****Ab Type** gp120 V2**Research Contact** Susan Zolla-Pazner**References** Gorny *et al.* 2005; Pinter *et al.* 2004; Ling *et al.* 2004; Gorny & Zolla-Pazner 2004; Ling *et al.* 2002; Nyambi *et al.* 2000**Keywords** antibody binding site definition and exposure, co-receptor, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 830A: 2909 is a human anti-Env NAb that was selected by neutralization assay and binds to the quaternary structure on the intact virion. ELISA-based competition assays and subsequent mutational analysis determined that the CD4BS and V2 and V3 loops contribute to the 2909 epitope: 2909 binding was inhibited by MAbs 447-52d (anti-V3), 830A (anti-V2), and IgG1b12 (anti-CD4BS) and sCD4. 2909 was not inhibited by MAbs 670, 1418, nor 2G12. Gorny *et al.* [2005]
- 830A: This broad review of anti-Envelope MAbs notes that V2 MAbs are generally weakly neutralizing at best, and somewhat strain specific. 830A neutralizes SF162. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 830A: The role of serine proteases on HIV infection was explored. Trypsin decreased the binding of most Env MAb tested and diminished cell fusion of H9 cells infected with HIV-1 LAI virus (H9/IIIB) to MAGI cells. In contrast, thrombin increased the binding of MAbs to gp120 epitopes near the CD4 and CCR5 binding sites, and increased cell fusion. Binding of 17b and F105 was decreased by trypsin, but increased by thrombin. V2 MAbs 830A and 2158 were decreased by trypsin, unaffected by thrombin. Thrombin may increase HIV-induced cell fusion in blood by causing a conformational activating shift in gp120. Ling *et al.* [2004] (**antibody binding site definition and exposure**)
- 830A: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. Three anti-V2 MAb were tested – both 2158 and 830A bound more strongly to JRFL, but neutralized SF162, and did not neutralize JRFL. Thus V2 domains are better neutralization targets in SF162. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 830A: A pseudotyping assay showed that an X4 V3 loop peptide could enhance infectivity of X4 virus, R5 and R5X4 V3 loops peptides could enhance infectivity of an R5 virus, and R5X4 peptides could enhance infectivity of an R5X4 virus. Neither R5 nor R5X4 peptides influenced binding of CD4BS MAbs F105 and Ig1Gb12, but did increase binding of CD4i MAb 17b. Of three V2 MAbs, only 830A, not 2158 or 1357 was enhanced by V3 peptide binding. Ling *et al.* [2002] (**antibody binding site definition and exposure, co-receptor**)
- 830A: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 anti-V2 MAbs, which showed weak and sporadic binding, with the most frequent binding to C and D clades. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 1256**MAb ID** CRA-3 (CRA3)**HXB2 Location** Env**Author Location** gp120

**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)** mouse (IgG2a)  
**Ab Type** gp120 V2  
**Research Contact** Mark Page, NIBSC AIDS reagent project,  
 Potters Bar, Herts, UK  
**References** Holl *et al.* 2006a; Ditzel *et al.* 1997; Moore  
 & Sodroski 1996; Shotton *et al.* 1995; Thali  
*et al.* 1993; Moore *et al.* 1993a; Moore & Ho  
 1993

**Keywords** dendritic cells, neutralization

- CRA-3: UK Medical Research Council AIDS reagent: ARP324.
- CRA3: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- CRA-3: Many MAbs enhance binding, including some anti-C5, C1, V4, and C4 MAbs – enhances binding of only a small number of anti-V3 loop MAbs. Moore & Sodroski [1996]
- CRA-3: Called CRA3 – Same competition group as CRA6. Shotton *et al.* [1995]
- CRA-3: Conformational, does not bind well to denatured gp120. Moore & Ho [1993]
- CRA-3: specific for BH10 or HXB2, does not bind to MN, RF, or SF-2 gp120 – binding inhibited by deletion of the V2 loop, and the following amino acid substitutions: 176/177 FY/AT, 179/180 LD/DL, 183/184 PI/SG, and 192-194 YSL/GSS – epitope probably involves stem of V1/V2 loop structure. Moore *et al.* [1993a]

**No.** 1257

**MAb ID** CRA-4 (CRA4)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L (HXB2)

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120 V2

**Research Contact** Mark Page, NIBS, MRC AIDS reagent repository, ARP 325

**References** Holl *et al.* 2006a; Moore & Sodroski 1996; Shotton *et al.* 1995; Thali *et al.* 1993; Moore *et al.* 1993a; Moore & Ho 1993; McKeating *et al.* 1993b

**Keywords** dendritic cells, neutralization

- CRA-4: UK Medical Research Council AIDS reagent: ARP325.
- CRA-4: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- CRA-4: The only MAbs that enhanced binding were anti-V3 MAb 5G11 and anti-C1 MAb 135/9 binding – reciprocal inhibition of anti-V2 MAbs. Moore & Sodroski [1996]

- CRA-4: Cross-competes with MAbs 11/68b, 62c, 66c, 66a – similar to 66c and 66a – non-reciprocal inhibition by MAbs 12b, 60b and CRA-6. Shotton *et al.* [1995]
- CRA-4: Changes at residues 191/192/193 (YSL/GSS) within V2, 435 (Y/H) in C4, abrogate binding – type-specific neutralization. McKeating *et al.* [1993b]
- CRA-4: Conformational, does not bind well to denatured gp120. Moore & Ho [1993]
- CRA-4: Specific for BH10 and HXB2, does not bind to MN, RF, or SF-2 gp120 – binding inhibited by deletion of the V2 loop, and the following amino acid substitutions: 176/177 FY/AT, 179/180 LD/DL, 183/184 PI/SG, and 192-194 YSL/GSS. Moore *et al.* [1993a]

**No.** 1258

**MAb ID** L17

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 V2

**References** Gorny & Zolla-Pazner 2004; Kwong *et al.* 2002; Parren *et al.* 1998a; Ditzel *et al.* 1997

**Keywords** antibody binding site definition and exposure, binding affinity, review, variant cross-recognition or cross-neutralization

- L17: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weakly with limited cross-reactivity. L15 and L17 are Fabs specific for V2. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, review**)
- L17: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- L17: The rank order of Fab binding affinity to monomeric gp120 (Loop 2 > 3B3 > b12 = DO8i > b11 > b3 > b14 > b13 > DO142-10 > DA48 > L17) was markedly different than Fab

binding affinity to the mature oligomeric form (3B3 > b12 > DO142-10 > Loop 2 > b11 > L17 > b6 > DO8i > b14 > DA48 > b3 > b13) and binding to oligomeric form and neutralization were correlated for both Fabs and MAbs – authors suggest that neutralization is determined by the fraction of Ab sites occupied on a virion irrespective of the epitope. Parren *et al.* [1998a] (**binding affinity**)

**No.** 1259

**MAb ID** SC258 (52-581-SC258)

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB  
*HIV component:* gp120

**Species (Isotype)** mouse

**Ab Type** gp120 V2

**Research Contact** Gerry Robey, Abbott Laboratories

**References** He *et al.* 2002; Ditzel *et al.* 1997; Trkola *et al.* 1996a; Moore & Sodroski 1996; Ditzel *et al.* 1995; Moore *et al.* 1994b; Yoshiyama *et al.* 1994; Gorny *et al.* 1994; Thali *et al.* 1993; Moore *et al.* 1993a

- SC258: Transgenic mice carrying human genes allowing production of fully human MAbs were used to rapidly create a panel of anti-HIV gp120 MAb producing hybridomas by immunization with HIV SF162 gp120 – the previously described human MAbs 5145A(CD4BS), 4117C (plus others, V3) and 697D (and SC258, V2) were used as controls. He *et al.* [2002]
- SC258: Several MAbs binding to various gp120 epitopes enhance binding, but the only MAb that SC258 enhanced binding of was anti-CD4 binding site MAb F91 – reciprocal inhibition with V2 region antibodies. Moore & Sodroski [1996]
- SC258: Does not inhibit gp120 interaction with CCR-5 in a MIP-1beta-CCR-5 competition study – listed as not neutralizing. Trkola *et al.* [1996a]
- SC258: Does not compete with IgG1b12 – reciprocal inhibition with MAbs L39, L40, and L78. Ditzel *et al.* [1995]
- SC258: Very poor reactivity with gp120 molecules outside of clade B. Moore *et al.* [1994b]
- SC258: HIV-1 RF V2 substitutions 177 Y/H and 179 L/P in the V2 loop of RF reduce affinity – 177 Y/H inhibits SC258 neutralization. Yoshiyama *et al.* [1994]
- SC258: Called 52-581-SC258 – binds to BH10, MN, and RF gp120 – neutralizes BH10 – binding inhibited by deletion of the V2 loop, and the following amino acid substitutions: 176/177 FY/AT, 179/180 LD/DL, 183/184 PI/SG, and 192-194 YSL/GSS. Moore *et al.* [1993a]

**No.** 1260

**MAb ID** L25

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L (weak)

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1)

**Ab Type** gp120 V2-CD4BS

**References** Gorny & Zolla-Pazner 2004; Parren *et al.* 1997b; Ditzel *et al.* 1997; Ditzel *et al.* 1995

**Keywords** antibody binding site definition and exposure, review, variant cross-recognition or cross-neutralization

- L25: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weakly with limited cross-reactivity. L25, L39, L40 and L78 are Fabs specific for a complex binding site involving V2 and elements of the sCD4 binding site regions; among these only L25 and L78 mediate weak neutralization of some TCLA strains. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, review**)
- L25: gp120 immobilized on solid phase by capture with anti-CD4 BS MAb L72 was used for selection of Fabs – a single anti-V2-CD4 BS Fab was obtained with sensitivity to substitutions in the V2 and CD4 BS regions – rodent anti-V2 MAb SC258 competes with L25. Ditzel *et al.* [1997]
- L25: Neutralizes TCLA strains weakly, but not primary isolates. Parren *et al.* [1997b]

**No.** 1261

**MAb ID** L39

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp120 V2-CD4BS

**References** Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995

**Keywords** antibody binding site definition and exposure, review, variant cross-recognition or cross-neutralization

- L39: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weakly with limited cross-reactivity. L25, L39, L40 and L78 are Fabs specific for a complex binding site involving V2 and elements of the sCD4 binding site regions; among these only L25 and L78 mediate weak neutralization of some TCLA strains. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, review**)
- L39: This Fab does not inhibit sCD4 binding, but is inhibited by sCD4, probably due to conformational changes – it is competed by anti-V2 MAbs, and sensitive to amino acid substitutions in the V3 loop (similar patterns were observed for L39 and L78 gp120 amino acid substitutions enhancing or reducing binding) – does not compete with CD4BS MAbs, but is sensitive to amino acid changes at positions 368 and 370 – binding unaffected by deglycosylation – reciprocal inhibition with V2 MAbs SC258 and 684-238 – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995]

**No.** 1262

**MAb ID** L40

**HXB2 Location** Env

**Author Location** gp120

- Epitope**  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp120 V2-CD4BS  
**References** Gorny & Zolla-Pazner 2004; Ditzel *et al.* 1995  
**Keywords** antibody binding site definition and exposure, responses in children, variant cross-recognition or cross-neutralization
- L40: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weakly with limited cross-reactivity. L25, L39, L40 and L78 are Fabs specific for a complex binding site involving V2 and elements of the sCD4 binding site regions; among these only L25 and L78 mediate weak neutralization of some TCLA strains. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, responses in children**)
  - L40: This Fab does not inhibit sCD4 binding, but is inhibited by sCD4, probably due to conformational changes – it is competed by anti-V2 MAbs, and sensitive to amino acid substitutions in the V3 loop (similar patterns were observed for L40 and L78 gp120 amino acid substitutions enhancing or reducing binding) – does not compete with CD4BS MAbs, but is sensitive to amino acid changes at positions 368 and 370 – binding only partially affected by deglycosylation – reciprocal inhibition with V2 MAbs SC258 and 684-238 – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995]

No. 1263

**MAb ID** L78**HXB2 Location** Env**Author Location** gp120**Epitope****Neutralizing** L**Immunogen** HIV-1 infection**Species (Isotype)** human (IgG1κ)**Ab Type** gp120 V2-CD4BS**References** Gorny & Zolla-Pazner 2004; Kwong *et al.* 2002; Ditzel *et al.* 1995**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, review, variant cross-recognition or cross-neutralization

- L78: In a review of Envelope binding MAbs in this database, V2-specific MAbs are noted to have some ability to neutralize HIV-1, but generally weakly with limited cross-reactivity. L25, L39, L40 and L78 are Fabs specific for V2 that are also associated with sCD4 binding site regions; among these only L25 and L78 mediate weak neutralization of some TCLA strains. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, review**)
- L78: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb

- ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- L78: Substitutions at V2: (152/153 GE/SM, 183/184 PI/SG, 191/193 YL/GS), 262 N/T, V3 (314 G/W), CD4BS (257 T/R, 368 D/R, 370 E/R) inhibit binding, and some C4 and C5 substitutions enhance binding – this Fab does not inhibit sCD4 binding, but is inhibited by sCD4, probably due to conformational changes – it is competed by anti-V2 MAbs, and sensitive to amino acid substitutions in the V3 loop – does not compete with CD4BS MAbs, but is sensitive to amino acid changes at positions 368 and 370 – Fab neutralizes MN and LAI – binding unaffected by deglycosylation – reciprocal inhibition with V2 MAbs SC258 and 684-238 – heavy and light chain variable region sequence is available. Ditzel *et al.* [1995] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, antibody sequence variable domain**)

No. 1264

**MAb ID****HXB2 Location** Env**Author Location** gp120**Epitope****Subtype** A, B, C**Neutralizing****Immunogen** HIV-1 infection**Species (Isotype)** human**Ab Type** gp120 V3**References** Gilljam *et al.* 1999

- Sera from individuals with infections of HIV-1 subtype A-E were tested against purified proteins from primary PBMC cultures. Sera reactivity tended not to be strongly related to subtype, rather probably reflected the sum of reactivities to conserved and variable regions in the proteins. V3 peptide comparisons showed some preference for within subtype binding. Gilljam *et al.* [1999]

No. 1265

**MAb ID** 10D8**HXB2 Location** Env**Author Location** gp160 (V3) (303–338)**Epitope****Subtype** B

**Neutralizing  
Immunogen****Species (Isotype)** human**Ab Type** gp120 V3**References** Callahan *et al.* 1991

- 10D8: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interactions mediated through the local high positive charge density in the V3 loop. The binding of this anti-V3 antibody is inhibited by dextran sulfate. Callahan *et al.* [1991]

**No.** 1266**MAB ID** 10F6**HXB2 Location** Env**Author Location** gp160 (V3) (303–338)**Epitope****Subtype** B**Neutralizing  
Immunogen****Species (Isotype)** human**Ab Type** gp120 V3**References** Callahan *et al.* 1991

- 10F6: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interactions mediated through the local high positive charge density in the V3 loop. The binding of this anti-V3 antibody is inhibited by dextran sulfate. Callahan *et al.* [1991]

**No.** 1267**MAB ID** 110J**HXB2 Location** Env**Author Location** gp120**Epitope****Neutralizing  
Immunogen****Species (Isotype)****Ab Type** gp120 V3**Research Contact** F. Traincard, Pasteur Institute, France**References** Moore & Sodroski 1996; Thali *et al.* 1993

- 110.J: Binds to carboxy-terminal side of the V3 loop – reciprocal binding inhibition with other anti-V3 and anti-C4 MABs – and reciprocal enhanced binding of some anti-V2 MABs and anti-CD4 binding site MABs. Moore & Sodroski [1996]
- 110.J: Inhibits sCD4-inducible anti-CD4 binding site MAB 48d. Thali *et al.* [1993]

**No.** 1268**MAB ID** 11G5**HXB2 Location** Env**Author Location** gp160 (V3) (303–338)**Epitope****Subtype** B**Neutralizing  
Immunogen****Species (Isotype)** human**Ab Type** gp120 V3**References** Callahan *et al.* 1991

- 11G5: Polyanionic polysaccharides were proposed to inhibit viral functions such as binding and syncytia formation through interactions mediated through the local high positive charge density in the V3 loop. The binding of this anti-V3 antibody is inhibited by dextran sulfate. Callahan *et al.* [1991]

**No.** 1269**MAB ID** 2182**HXB2 Location** Env**Author Location** (JRCSF)**Epitope****Subtype** B**Neutralizing** P**Immunogen** HIV-1 infection**Species (Isotype)** human (IgG1 $\lambda$ )**Ab Type** gp120 V3**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)**References** Pinter *et al.* 2004; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 2182: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MABs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally sensitive, suggesting some structural conservation despite sequence variation. These MABs have distinct epitopes relative to 447-52D, a MAB directed at the tip of the V3 loop that also can neutralize many primary isolates. Inter-clade cross-neutralization by these anti-V3 MABs is reduced. Gorny & Zolla-Pazner [2004] (**review, subtype comparisons**)
- 2182: V3 MAB neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MABs selected using V3 peptides neutralize less effectively than V3 MABs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAB was selected using a JR-CSF fusion protein, and could neutralize 6/13 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2182: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MABs, while SF162 is sensitive. All MABs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MABs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MABs had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigpgrafyTtgE for JR-FL and TigpgrafyAtgD for SF162). Only the V3 MAB that had a different affinity was 2182, which bound to JRFL with higher affinity. Even 2182



preferentially neutralized SF162, however, the JRFL gp120 backbone with the SF162 V1V2 region was the more neutralization sensitive than pure SF162. Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)

- 2182: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterohybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MAbs were each generated from different subjects – 2182 bound to 8/16 of the diverse isolates, not to any clade C or CRF01. Gorny *et al.* [2002] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1270

MAb ID 2191

HXB2 Location Env

Author Location (JRCSF)

Epitope

Subtype B

Neutralizing P

Immunogen HIV-1 infection

Species (Isotype) human (IgG1 $\lambda$ )

Ab Type gp120 V3

Research Contact Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

References Pinter *et al.* 2005; Pinter *et al.* 2004; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002

Keywords antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 2191: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potentially neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MAbs 4117c, 2219, 2191, and 447-52D, but only had minor

effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MAbs IgG1b12, 2G12, and 2F5. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)

- 2191: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally sensitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Inter-clade cross-neutralization by these anti-V3 MAbs is reduced. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review, subtype comparisons**)
- 2191: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using a JR-CSF fusion protein, and could neutralize 8/13 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2191: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MAbs, including 2191, had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HiggpgrafyTtgE for JR-FL and TigpgrafyAtgD for SF162). Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 2191: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterohybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently

living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MABs were each generated from different subjects – 2191 bound to 10/16 of the diverse isolates, not to any clade D or CRF01. Gorny *et al.* [2002] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 1271  
**MAB ID** 2219  
**HXB2 Location** Env  
**Author Location** (JRCSF)  
**Epitope**  
**Subtype** B  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**Ab Type** gp120 V3  
**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)  
**References** Pinter *et al.* 2005; Pinter *et al.* 2004; Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002  
**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 2219: This study is about the V2 MAb C108g, that is type-specific and neutralizes BaL and HXB2. JR-FL is a neutralization resistant strain; modification of JRFL at V2 positions 167 and 168 (GK->DE) created a C108g epitope, and C108g could potentially neutralize the modified JR-FL. The modification in V2 also increased neutralization sensitivity to V3 MABs 4117c, 2219, 2191, and 447-52D, but only had minor effects on neutralization by CD4BS MAb 5145A, and broadly neutralizing MABs IgG1b12, 2G12, and 2F5. Binding to CCR5 was completely inhibited by two V3 MABs, 4117C and 2219, and was substantially inhibited by 2G12, but was not inhibited by C108g. Pinter *et al.* [2005] (**antibody binding site definition and exposure**)
- 2219: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MABs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally sensitive, suggesting some structural conservation despite sequence variation. These MABs have distinct epitopes relative to 447-52D, a MAB directed at the tip of the V3 loop that also can neutralize many primary isolates. Interclade cross-neutralization by these anti-V3 MABs is reduced. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review, subtype comparisons**)
- 2219: V3 MAB neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MABs selected using V3 peptides neutralize less effectively than V3 MABs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAB was selected using a JR-CSF fusion protein, and could neutralize 6/13 B

clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

- 2219: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MABs, while SF162 is sensitive. All MABs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MABs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MABs, including 2219, had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigpgrafyTtgE for JR-FL and TigpgrafyAtgD for SF162). Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 2219: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MABs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MABs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MABs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MABs were used as controls: anti-V3 447-52D (anti-V3 MAB for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAB control), 1331A (anti-C5 used as a linear binding site MAB control), MAb 246 (anti-gp41 MAB that bound to primary isolates of all clades) – 5/6 MABs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MABs were each generated from different subjects – 2219 bound to 13/16 of the diverse isolates. Gorny *et al.* [2002] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 1272  
**MAB ID** 2412  
**HXB2 Location** Env  
**Author Location** gp120 (V3) (JRCSF)  
**Epitope**  
**Subtype** B  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**Ab Type** gp120 V3  
**Research Contact** Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)  
**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 2412: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally sensitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Interclade cross-neutralization by these anti-V3 MAbs is reduced. Gorny & Zolla-Pazner [2004] (**antibody binding site definition and exposure, review**)
- 2412: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using a JR-CSF fusion protein, and could neutralize 4/13 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2412: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterhybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MAbs were each generated from different subjects – 2412 bound to 7/16 of the diverse isolates, and did not bind to any of the clade C, D or CRF01 viruses. Gorny *et al.* [2002] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

No. 1273

MAb ID 2442

HXB2 Location Env

Author Location (JRCSF)

Epitope

**Subtype B**

**Neutralizing P**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp120 V3

**Research Contact** Susan Zolla-Pazner (Zollas01@mccr6.med.nyu) (NYU Med. Center)

**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review, variant cross-recognition or cross-neutralization

- 2442: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally sensitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Interclade cross-neutralization by these anti-V3 MAbs is reduced. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 2442: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using a JR-CSF fusion protein, and could neutralize 9/13 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2442: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterhybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MAbs were each generated from different subjects – 2442 bound to 13/16 of the diverse isolates. Gorny *et al.* [2002] (**antibody binding**)

**site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, review)**

**No.** 1274  
**MAb ID** 2456  
**HXB2 Location** Env  
**Author Location** (JRCSF)  
**Epitope**  
**Subtype** B  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1 $\lambda$ )  
**Ab Type** gp120 V3  
**Research Contact** Susan Zolla-Pazner (Zollas01@mccr6.med.nyu) (NYU Med. Center)  
**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Gorny *et al.* 2002  
**Keywords** antibody binding site definition and exposure, review

- 2456: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. The set that can cross-neutralize primary isolates (2182, 2191, 2219, 2412, 2442, 2456) bind V3 but are conformationally sensitive, suggesting some structural conservation despite sequence variation. These MAbs have distinct epitopes relative to 447-52D, a MAb directed at the tip of the V3 loop that also can neutralize many primary isolates. Inter-clade cross-neutralization by these anti-V3 MAbs is reduced. Gorny & Zolla-Pazner [2004] (review)
- 2456: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using a JR-CSF fusion protein, and could neutralize 4/12 B clade viruses. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 2456: Conformation-dependent anti-V3 loop Abs may be more cross-reactive, so six new V3 MAbs were generated from cells of asymptomatic HIV-1-infected individuals by selection of heterohybridomas using a V3-fusion protein (V3-fp), the HIV-1 JRCSF V3 loop inserted into a truncated murine leukemia virus gp70 – the six new MAbs all bind to the tip of the V3 loop and cross-compete with the MAb 447-52D and are conformationally sensitive – MAbs showed cross-clade binding to native, intact virions of clades A(N=2), B(N=4), and F(N=2), limited binding to C(N=3) and D(N=3), and did not bind to CRF01(subtype E, N=2) – the strength binding was highly correlated with percent neutralization using the ghost cell or PHA blast assay – five well-characterized MAbs were used as controls: anti-V3 447-52D (anti-V3 MAb for competition and neutralization studies), 654 (anti-CD4BS used as a conformation-sensitive MAb control), 1331A (anti-C5 used as a linear binding site MAb control), MAb 246 (anti-gp41 MAb that bound to primary isolates of all clades) – 5/6 MAbs were derived from individuals infected in the US, presumably with clade B, and one, 2182, was derived from an individual who

was infected abroad with clade A who is presently living in New York city – 2412 and 2456 were produced from cells obtained from the same individual, while the other MAbs were each generated from different subjects – 2456 bound to 12/16 of the diverse isolates. Gorny *et al.* [2002]

**No.** 1275  
**MAb ID** 2483  
**HXB2 Location** Env  
**Author Location** Env (JR-CSF)  
**Epitope**  
**Subtype** B  
**Neutralizing** P  
**Immunogen**  
**Species (Isotype)** human  
**Ab Type** gp120 V3  
**Research Contact** Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu  
**References** Gorny *et al.* 2004  
**Keywords** antibody binding site definition and exposure

- 2483: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This antibody was selected using a JRCSF fusion protein. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

**No.** 1276  
**MAb ID** 2497  
**HXB2 Location** Env  
**Author Location** Env (JR-CSF)  
**Epitope**  
**Subtype** B  
**Neutralizing** P  
**Immunogen**  
**Species (Isotype)** human  
**Ab Type** gp120 V3  
**Research Contact** Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu  
**References** Gorny *et al.* 2004  
**Keywords** antibody binding site definition and exposure

- 2497: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This antibody was selected using a JRCSF fusion protein. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

**No.** 1277  
**MAb ID** 2557  
**HXB2 Location** Env  
**Author Location** Env (JR-CSF)  
**Epitope**  
**Subtype** A, CRF02\_AG  
**Neutralizing** P  
**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 V3

**Research Contact** Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu

**References** Krachmarov *et al.* 2005; Gorny *et al.* 2004

**Keywords** antibody binding site definition and exposure, subtype comparisons, variant cross-recognition or cross-neutralization

- 2557: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. 2557 was derived from a person infected with a clade A or CRF02 virus, and binds to A and B V3 loops. Neutralization of JR-FL and SF162(UG V3) by anti-V3 MAbs 2557, 2558, 2601, but not subtype A primary isolates despite binding to the subtype A V3 loops, suggested masking by V1V2 blocking of neutralization by these antibodies. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons**)
- 2557: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This antibody was selected using a JRCSF fusion protein. Gorny *et al.* [2004]

**No.** 1278

**MAb ID** 2558

**HXB2 Location** Env

**Author Location** Env (92UG037)

**Epitope**

**Subtype** A, CRF02\_AG

**Neutralizing** P

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 V3

**Research Contact** Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu

**References** Krachmarov *et al.* 2005; Gorny *et al.* 2004

**Keywords** antibody binding site definition and exposure, subtype comparisons, variant cross-recognition or cross-neutralization

- 2558: Sera from subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B V3s. Sera from Cameroon did not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. 2557 was derived from a person infected with a clade A or CRF02 virus, and binds to A and B V3 loops. Neutralization of JR-FL and SF162(UG V3) by anti-V3 MAbs 2557, 2558, 2601, but not subtype A primary isolates despite binding to the subtype A V3 loops, suggested masking by

V1V2 blocking of neutralization by these antibodies. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons**)

- 2558: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This antibody was selected using an A clade fusion protein, 92UG037. It is unusual in that it is a V3 antibody selected for conformational aspects using an A clade virus, with a V3 GPGQ tip – clade B viruses are usually used and have GPGR tips. It cross-neutralizes and binds B clade HIV SF162. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

**No.** 1279

**MAb ID** 2580

**HXB2 Location** Env

**Author Location** Env (JR-CSF)

**Epitope**

**Subtype** B

**Neutralizing** P

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 V3

**Research Contact** Dr. Zolla-Pazner, Veterans Affairs Center, NY, NY. zollas01@endeavor.med.nyu.edu

**References** Gorny *et al.* 2004

**Keywords** antibody binding site definition and exposure

- 2580: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This antibody was selected using a JRCSF fusion protein. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)

**No.** 1280

**MAb ID** 391/95-D

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 V3

**Research Contact** S. Zolla-Pasner

**References** Guillon *et al.* 2002a

**Keywords** co-receptor, enhancing activity

- 391/95-D: This antibody was used to explore the sensitivity of chimeric envelope viruses to Ab-mediated enhancement or neutralization. V3 mediated enhancement and envelopes susceptible to enhancement used CCR5. Enhancement was CD4 dependent. Guillon *et al.* [2002a] (**co-receptor, enhancing activity**)

- No.** 1281  
**MAb ID** 39F  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)**  
**Ab Type** gp120 V3  
**Research Contact** James Robinson, Tulane University, New Orleans, LA, USA  
**References** Haynes *et al.* 2006; Liao *et al.* 2006; Selvarajah *et al.* 2005; Pantophlet *et al.* 2004; Kwong *et al.* 2002; Grundner *et al.* 2002; Yang *et al.* 2002  
**Keywords** antibody binding site definition and exposure, binding affinity, neutralization, subtype comparisons, vaccine antigen design, vaccine-specific epitope characteristics
- 39F: 29 subtype B V3 peptides were designed and used for immunization of guinea pigs. Peptides that induced Abs that neutralized more than 3 HIV isolates were shown to bind to this Ab better than peptides unable to induce neutralization of any of the HIV-1 primary isolates. Haynes *et al.* [2006] (**neutralization, binding affinity**)
  - 39F: The gp140 $\delta$ CFI protein of CON-S M group consensus protein and gp140CFI and gp140CF proteins of CON6 and WT viruses from HIV-1 subtypes A, B and C were expressed in recombinant vaccinia viruses and tested as immunogens in guinea pigs. 39F was shown to bind specifically to all recombinant proteins except for the gp140 $\delta$ FI derived from subtype C virus. The specific binding of this Ab to CON-S indicated that its conformational epitope was intact. 39F also bound specifically to the two subtype B gp120 proteins tested. Liao *et al.* [2006] (**antibody binding site definition and exposure, vaccine antigen design, subtype comparisons**)
  - 39F: Antigens were designed to attempt to target immune responses toward the IgG1b12 epitope, while minimizing antibody responses to less desirable epitopes. One construct had a series of substitutions near the CD4 binding site (GDMR), the other had 7 additional glycans (mCHO). The 2 constructs did not elicit b12-like neutralizing antibodies, but both antigens successfully dampened other responses that were intended to be dampened, while not obscuring b12 binding. V3 MAbs (447-52D, 19b, F245-B4e8 and 39F) bound to the GDMR antigen, but either did not bind or had diminished binding to mCHO. Selvarajah *et al.* [2005] (**vaccine antigen design, vaccine-specific epitope characteristics**)
  - 39F: By adding N-linked glycosylation sites to gp120, epitope masking of non-neutralizing epitopes can be achieved leaving the IgG1b12 binding site intact. This concept was originally tested with the addition of four glycosylation sites, but binding to b12 was reduced. It was modified here to exclude the C1 N-terminal region, and to include only three additional glycosylation sites. This modified protein retains full b12 binding affinity and it masks other potentially competing epitopes, and does not bind to 21 other MAbs to 7 epitopes on gp120, including 39F. To inhibit 39F binding, Arg 304 and Lys 305

had to be changed to Ala. Pantophlet *et al.* [2004] (**vaccine antigen design**)

- 39F: HIV-1 gp160 $\delta$ CT (cytoplasmic tail-deleted) proteoliposomes (PLs) containing native, trimeric envelope glycoproteins from R5 strains YU2 and JRFL, and X4 strain HXBc2, were made in a physiologic membrane setting as candidate immunogens for HIV vaccines – 2F5 bound to gp160 $\delta$ CT with a reconstituted membrane ten-fold better than the same protein on beads – anti-CD4BS MAbs IgG1b12 and F105, A32 (C1-C4), C11 (C1-C5), and 39F (V3) MAbs bound gp160 $\delta$ CT PLs indistinguishably from gp160 $\delta$ CT expressed on the cell surface. Grundner *et al.* [2002]
- 39F: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120 Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)
- 39F: Uncleaved soluble gp140 (YU2 strain, R5 primary isolate) can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif or using a T4 trimeric motif derived from T4 bacteriophage fibrin – stabilized oligomer gp140  $\delta$ 683(-FT) showed strong preferential recognition by NAbs IgG1b12 and 2G12 relative to the gp120 monomer, in contrast to poorly neutralizing MAbs F105, F91, 17b, 48d, and 39F which showed reduced levels of binding, and C11, A32, and 30D which did not bind the stabilized oligomer. Yang *et al.* [2002]

- No.** 1282  
**MAb ID** 4148d  
**HXB2 Location** Env  
**Author Location** Env  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**  
**Ab Type** gp120 V3  
**Research Contact** Abraham Pinter, Public Health Research Institute, Newark, NJ, 07103. pinter@phri.org  
**References** Pinter *et al.* 2004; Pinter *et al.* 1993b

**Keywords** antibody generation, variant cross-recognition or cross-neutralization

- 4148D: V1V2 was determined to be the region that conferred the neutralization phenotype differences between two R5-tropic primary HIV-1 isolates, JRFL and SF162. JRFL is resistant to neutralization by many sera and MAbs, while SF162 is sensitive. All MAbs tested, anti-V3, -V2, -CD4BS, and -CD4i, (except the broadly neutralizing MAbs IgG1b12, 2F5, and 2G12, which neutralized both strains), neutralized the SF162 pseudotype but not JRFL, and chimeras that exchanged the V1V2 loops transferred the neutralization phenotype. 5/6 anti-V3 MAbs, including 4148D, had similar binding affinity to soluble SF162 and JR-FL rgp120s, although the V3 loop differs at three positions (HigpgrafyTtgE for JR-FL and TigpgrafyAtgD for SF162). Pinter *et al.* [2004] (**variant cross-recognition or cross-neutralization**)
- 4148D: Pinter1993a first describes this MAb. Pinter *et al.* [1993b] (**antibody generation**)

**No.** 1283

**MAb ID** 55/68b

**HXB2 Location** Env

**Author Location** gp120 (300–315)

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)**

**Ab Type** gp120 V3

**References** Peet *et al.* 1998

- 55/68b: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, and anti-V3 MAb 55/68b binding was abrogated by V3 serine substitutions in the V3 loop – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

**No.** 1284

**MAb ID** 5G11

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)**

**Ab Type** gp120 V3

**Research Contact** S. Nigida and L. Arthur, NCI, Frederick, MD USA

**References** Moore & Sodroski 1996

- 5G11: Binds to conformation sensitive epitope in the V3 loop – reciprocal inhibition of other V3 loop MAbs – reciprocal enhancement of some C1–C5 MAbs (unusual for an anti-V3 MAb) and CD4 binding site MAbs – and enhances binding of V2 MAbs. Moore & Sodroski [1996]

**No.** 1285

**MAb ID** 6.1

**HXB2 Location** Env

**Author Location** gp120 (SF162)

**Epitope**

**Subtype B**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162

*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V3

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** review

- 6.1: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. 6.1 was non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 6.1: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – 3/4 V3 MAbs bound a similar linear epitope between positions 11–30 of the MN V3 loop (8E11/A8, 6.1, and 6.7), but only 8E11/A8 could weakly neutralize autologous strain SF162. He *et al.* [2002]

**No.** 1286

**MAb ID** 6.7

**HXB2 Location** Env

**Author Location** gp120 (SF162)

**Epitope**

**Subtype B**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade SF162

*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)

**Species (Isotype)** transgenic mouse (IgG2κ)

**Ab Type** gp120 V3

**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org

**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002

**Keywords** antibody binding site definition and exposure, antibody generation, review

- 6.7: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. 6.7 was non-neutralizing. Gorny & Zolla-Pazner [2004] (**review**)
- 6.7: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – 3/4 V3 MAbs bound a similar linear epitope between positions 11–30 of the MN V3 loop (8E11/A8, 6.1, and 6.7), but only 8E11/A8 could weakly neutralize autologous strain SF162. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation**)

**No.** 1287  
**MAb ID** 8.27.3  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** transgenic mouse (IgG2κ)  
**Ab Type** gp120 V3  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org  
**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002  
**Keywords** review, variant cross-recognition or cross-neutralization

- 8.27.3: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, like 8.27.3; a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**variant cross-recognition or cross-neutralization, review**)
- 8.27.3: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with HIV SF162 gp120 – 1/4 V3 MAbs, 8.27.3, bound a discontinuous epitope that was broadly cross-reactive with B clade R5 and X4 strains (not E clade) and could neutralize autologous strain SF162. He *et al.* [2002]

**No.** 1288  
**MAb ID** 8E11/A8  
**HXB2 Location** Env  
**Author Location** gp120 (SF162)  
**Epitope**  
**Subtype** B  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade SF162  
*HIV component:* gp120 *Adjuvant:* Ribi adjuvant (MPL+TDM) (RIBI)  
**Species (Isotype)** transgenic mouse (IgG2κ)  
**Ab Type** gp120 V3  
**Research Contact** Dr. Abraham Pinter, Public Health Research Institute, Newark, NJ, pinter@phri.org  
**References** Gorny & Zolla-Pazner 2004; He *et al.* 2002  
**Keywords** antibody binding site definition and exposure, antibody generation, autologous responses, review

- 8E11/A8: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 8E11/A8: Transgenic mice (strain XenoMouse G2) carrying human genes allowing production of fully human IgG2kappa MAbs were used to rapidly create a panel of anti-HIV gp120 MAb-producing hybridomas by immunization with

HIV SF162 gp120 – 3/4 V3 MAbs bound a similar linear epitope between positions 11-30 of the MN V3 loop (8E11/A8, 6.1, and 6.7), but only 8E11/A8 could weakly neutralize autologous strain SF162. He *et al.* [2002] (**antibody binding site definition and exposure, antibody generation, autologous responses**)

**No.** 1289  
**MAb ID** 9305  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen**  
**Species (Isotype)** mouse  
**Ab Type** gp120 V3  
**Research Contact** Du Pont, Wilmington DE  
**References** McDougal *et al.* 1996

**No.** 1290  
**MAb ID** A1g8  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1λ)  
**Ab Type** gp120 V3  
**Research Contact** James Robinson, Tulane University Med School, New Orleans, LA, USA  
**References** Cavacini *et al.* 2003; Cavacini *et al.* 2002  
**Keywords** antibody interactions, co-receptor, variant cross-recognition or cross-neutralization

- A1g8: The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. B4e8 enhanced binding of CD4i MAbs 4.8d, 1.7b, and A1g8 to R5X4 virus 92HT593, but only of 48d to the R5 virus 92US660, and there was only a modest impact of the combination of B4e8 and CD4i MAbs on neutralization. Cavacini *et al.* [2003] (**antibody interactions, co-receptor**)
- A1g8: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-V3 MAb B4a1 increased binding of CD4i MAbs 48d, 17b and A1g8, but only A1g8 binding was increased by B4a1 to the R5 isolate. Additive effects on neutralization of the R5X4 isolate with B4a1 and CD4i MAbs was observed, presumably due to increased exposure of the CD4i binding site, but not for the R5 isolate. Anti-gp41 MAb F240 had a synergistic effect on neutralization with CD4i MAbs 48d and 17b, but not with A1g8 for the R5X4 virus. Cavacini *et al.* [2002] (**antibody interactions, co-receptor, variant cross-recognition or cross-neutralization**)

**No.** 1291  
**MAb ID** AG1121 (1121)  
**HXB2 Location** Env  
**Author Location** gp120



**Epitope**  
**Neutralizing L**  
**Immunogen**

**Species (Isotype)****Ab Type** gp120 V3**Research Contact** AGMED, Inc, Bedford, MA, USA or ImmunoDiagnostics, Inc, Woburn, MA, USA**References** Si *et al.* 2001; Cao *et al.* 1997b; Sullivan *et al.* 1995

- AG1121: SHIV-HXBc2 is a neutralization sensitive non-pathogenic virus, and several *in vivo* passages through monkey's yielded highly pathogenic SHIV KU-1 – HXBc2 and the KU-1 clone HXBc2P3.2 differ in 12 amino acids in gp160 – substitutions in both gp120 and gp41 reduced the ability of sCD4, IgG1b12, F105 and AG1121 to Env achieve saturation and full occupancy, and neutralize KU-1 – 17b and 2F5 also bound less efficiently to HXBc2P3.2, although 2G12 was able to bind both comparably. Si *et al.* [2001]
- AG1121: Called 1121 – Virus with the V1-V2 loop deleted was viable and more susceptible to neutralization by CD4i MAb 17b, and anti-V3 MAbs 1121, 9284, and 110.4, but not to and CD4BS MAb F105 or sCD4. Cao *et al.* [1997b]
- AG1121: Recognizes monomeric gp120 from T-cell adapted line HXBc2 and primary isolate 89.6 equally well, but 89.6 was three-fold less sensitive to neutralization by AG1121 than HXBc2. Sullivan *et al.* [1995]

**No.** 1292**MAb ID** Ag1211**HXB2 Location** Env**Author Location** gp120 (V3) (JRFL)**Epitope****Neutralizing****Immunogen****Species (Isotype)****Ab Type** gp120 V3**References** Kwong *et al.* 2002**Keywords** antibody binding site definition and exposure

- Ag1211: Thermodynamics of binding to gp120 was measured using isothermal titration calorimetry for sCD4, 17b, b12, 48d, F105, 2G12 and C11 to intact YU2 and the HXBc2 core. The free energy of binding was similar, and not only CD4 but MAb ligands induced thermodynamic changes in gp120 that were independent of whether the core or the full gp120 protein was used. Non-neutralizing CD4BS and CD4i MAbs had large entropy contributions to free energy (mean: 26.1 kcal/mol) of binding to the gp120 monomer, except the potent CD4BS neutralizing MAb b6 had a much smaller value of 5.7 kcal/mol. High values suggest surface burial or protein folding and ordering of amino acids. Variable loop MAbs (L17, L78, 19b, 39F, Ag1211, D0142, and G3-2999) MAbs that bind to the N and C termini (211/c, A32, L100, P35, and C11) do not have dramatic entropy changes. These results suggest that while the trimeric Env complex has four surfaces, a non-neutralizing face (occluded on the oligomer), a variable face, a neutralizing face and a silent face (protected by carbohydrate masking), gp120 monomers further protect receptor binding sites by conformational or entropic masking, requiring a large energy handicap for Ab binding not faced by other anti-gp120

Abs. Kwong *et al.* [2002] (**antibody binding site definition and exposure**)**No.** 1293**MAb ID** B4a1**HXB2 Location** Env**Author Location** gp120 (V3)**Epitope****Subtype** B**Neutralizing****Immunogen** HIV-1 infection**Species (Isotype)** human**Ab Type** gp120 V3**Research Contact** James Robinson, Tulane University Med School, New Orleans, LA, USA**References** Cavacini *et al.* 2003; Cavacini *et al.* 2002**Keywords** antibody interactions, co-receptor, variant cross-recognition or cross-neutralization

- B4a1: The MAb B4e8 binds to the base of the V3 loop, neutralizes multiple primary isolates and was studied for interaction with other MAbs. The anti-V3 MAb B4a1 cross-competes with B4e8. Cavacini *et al.* [2003] (**antibody interactions**)
- B4a1: This study examined antibody interactions, binding and neutralization with a B clade R5 isolate (92US660) and R5X4 isolate (92HT593). Abs generally bound and neutralized the R5X4 isolate better than the R5 isolate. Anti-gp41 MAb F240 binding was not affected by the binding of the V3 loop MAb B4a1, but preincubation with F240 could enhance B4a1 binding of the R5 isolate. B4a1 reacts with many B clade isolates, and preincubation with sCD4 enhances binding to both the R5 and R5X4 isolates. B4a1 increased binding of CD4i MAbs 48d, 17b and A1g8, as well as CD4BS MAbs IgG1b12 and F105 to R5X4 virions, but only A1g8 and IgG1b12 binding was increased by B4a1 to the R5 isolate. Additive effects on neutralization of the R5X4 isolate with B4a1 and CD4i MAbs was observed, presumably due to increased exposure of the CD4i binding site, but not for the R5 isolate. B4a1 had an additive effect on neutralization with 2G12 with the R5X4 virus but not the R5 virus, and did not impact 2F5 neutralization. Cavacini *et al.* [2002] (**antibody interactions, co-receptor, variant cross-recognition or cross-neutralization**)

**No.** 1294**MAb ID** B4e8 (F425 B4e8)**HXB2 Location** Env**Author Location** gp120 (V3)**Epitope****Subtype** B**Neutralizing****Immunogen** HIV-1 infection**Species (Isotype)** human (IgG2κ)**Ab Type** gp120 V3**Research Contact** Lisa Cavacini, Beth Israel Deconess Medical Center, Boston MA, USA**References** Lusso *et al.* 2005; Zwick *et al.* 2003; Liu *et al.* 2003; Cavacini *et al.* 2003

**Keywords** antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, co-receptor, variant cross-recognition or cross-neutralization

- B4e8: The epitope for the MAb D19 is conserved and embedded in V3. D19 is unique in that for R5 viruses, it was cryptic and did not bind without exposure to sCD4, and for X4 and R5X4 isolates it was constitutively exposed. It had an overlapping binding region with MAbs 447-52D, B4e8, and 268-D, but different reactivity patterns and fine specificity. While B4e8 and 447-52D could bind to the R5 virus BaL in the absence of sCD4, treatment with sCD4 did increase the binding of both B4e8 and 447-52D, but did not impact their ability to neutralize BaL. Lusso *et al.* [2005] (**antibody binding site definition and exposure**)
- B4e8: This MAb binds to the base of the V3 loop, and binds and neutralizes multiple primary isolates. The anti-V3 MAb B4a1 cross-competes with B4e8. B4e8 and 2G12 enhanced each others binding, and gave synergistic neutralization. B4e8 could neutralize R5X4 virus 92HT593 better than 2G12, while 2G12 was better at neutralizing R5 virus 92US660. B4e8 enhanced binding of CD4i MAbs 4.8d, 1.7b, and A1g8 to 92HT593, but only of 48d to the 92US660, and there was only a modest impact of the combination of B4e8 and CD4i MAbs on neutralization. CD4BS MAb IgG1b12 had no effect on B4e8 binding. Anti-gp41 MAb F240 inhibited B4e8 neutralization. Cavacini *et al.* [2003] (**antibody binding site definition and exposure, antibody generation, antibody interactions, co-receptor, variant cross-recognition or cross-neutralization**)
- B4e8: The effect of isotype (IgG1 and IgG3) and subtype (IgA) switching of parental F425B4e8 (IgG2) on HIV-1 binding and neutralization was investigated. IgG1- and IgA-F425B4e8 mutants showed virus-specific binding levels and TCLA SF2 isolate compared to the parental IgG2. Comparable levels of neutralization of primary isolates 92HT593 (R5X4) and 92US660 (R5) was achieved by all isotypes and subtypes of F425B4e8. Liu *et al.* [2003] (**variant cross-recognition or cross-neutralization, antibody sequence variable domain**)
- B4e8: Called F425 B4e8. scFv 4KG5 reacts with a conformational epitope that is formed by the V1V2 and V3 loops and the bridging sheet (C4) region of gp120 and is influenced by carbohydrates. Of a panel of MAbs tested, only NAb b12 enhanced 4KG5 binding to gp120 JRFL. MAbs to the following regions diminished 4KG5 binding: V2 loop, V3 loop, V3-C4 region, CD4BS. MAbs directed against C1, CD4i, C5 regions didn't impact 4KG5 binding. These results suggest that the orientation or dynamics of the V1/V2 and V3 loops restricts CD4BS access on the envelope spike, and IgG1b12 can uniquely remain unaffected by these loops. This was one of the V3 MAbs used. Zwick *et al.* [2003] (**antibody interactions**)

No. 1295

MAB ID D27

HXB2 Location Env

Author Location gp120 (IIIB)

Epitope

### Neutralizing

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 V3

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Otteken *et al.* 1996; Earl *et al.* 1994

- D27: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D27 is one of two MAbs labeled group Ca, that was type-specific for BH8 – D27 fully blocked CD4 binding, and the deletion of the V3 loop abrogated binding. Sugiura *et al.* [1999]
- D27: Pulse label experiments of 4 MAbs (D20, D27, T20, and T22) binding to noncleavable gp160 revealed that these anti-CD4 MAbs bound with a delay, and that the epitope formed with a t 1/2 of about 10 minutes. Otteken *et al.* [1996]
- D27: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1296

MAB ID D47

HXB2 Location Env

Author Location gp120 (IIIB)

Epitope

Neutralizing

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* Env

**Species (Isotype)** mouse

**Ab Type** gp120 V3

**Research Contact** Patricia Earl, NIAID, NIH

**References** Salzwedel *et al.* 2000; Earl *et al.* 1997; Wyatt *et al.* 1997; Otteken *et al.* 1996; Richardson *et al.* 1996; Earl *et al.* 1994

**Keywords** antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization

- D47: sCD4 can activate fusion between effector cells expressing Env and target cells expressing coreceptor (CCR5 or CXCR4) alone without CD4 – V3 MAb D47 is strain specific and can inhibit sCD4 mediated infection, but only of the closely related LAV Env, while anti-CD4i MAbs were broadly cross-neutralizing. Salzwedel *et al.* [2000] (**variant cross-recognition or cross-neutralization**)
- D47: Used for comparison in a study of gp41 antibodies – D47 binds to a greater extent to cell surface expressed Env than any of 38 conformation dependent anti-gp41 MAbs. Earl *et al.* [1997]
- D47: Binds both gp120 and soluble gp120+gp41 complex efficiently, suggesting its gp120 epitope is not blocked by gp41 binding. Wyatt *et al.* [1997] (**antibody binding site definition and exposure**)
- D47: Pulse label experiments of MAb binding to noncleavable gp160 revealed that this anti-V3 MAb bound immediately and binding stayed constant through chase period. Otteken *et al.* [1996]

- D47: Used for capture of oligomeric Env for antigen capture ELISA – binding of this antibody to oligomeric Env IIIB was not blocked by human sera from the US, consistent with a low prevalence of IIIB-like V3 strains. Richardson *et al.* [1996] (**antibody binding site definition and exposure**)
- D47: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994] (**antibody generation**)

No. 1297

**MAb ID** D56

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing** L

**Immunogen** vaccinia

*Vector/Type:* vaccinia *Strain:* B clade IIIB

*HIV component:* oligomeric gp140

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 V3

**Research Contact** P. Earl, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

**References** Sugiura *et al.* 1999; Earl *et al.* 1994

- D56: A comparison of 25 gp120 specific, conformation dependent MAbs was done – D56 is one of two MAbs labeled group Ca, that was type-specific for BH8 – D56 fully blocked CD4 binding, and the deletion of the V3 loop abrogated binding – 12.5 ug/ml of D56 was required to achieve 50% neutralization of HIV-1 NL4-3. Sugiura *et al.* [1999]
- D56: Generated during a study of the influence of the oligomeric structure of Env in determining the repertoire of the Ab response. Earl *et al.* [1994]

No. 1298

**MAb ID** F5.5

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** mouse

**Ab Type** gp120 V3

**Research Contact** Hybridolabs, Institute Pasteur

**References** Altmeyer *et al.* 1999

- F5.5: A Semliki Forest virus (SFV) expression system carrying BX08 env was used to study the conformation of gp120 Env – intracytoplasmic gp120 was recognized by the anti-V3 MAbs K24 and F5.5, while gp120 at the plasma membrane was detected only by conformation dependent MAbs 2G12, 670-D and 694/98D and not V3 MAbs – expression in rat brain also showed that surface-expressed Env was recognized only by the conformation-dependent antibodies and not by anti-V3 antibodies. Altmeyer *et al.* [1999]

No. 1299

**MAb ID** G3-1472

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

### Immunogen

**Species (Isotype)**

**Ab Type** gp120 V3

**Research Contact** M. Fung

**References** Moore & Sodroski 1996

- G3-1472: Binds to carboxy-terminal side of the V3 loop – reciprocal binding inhibition with other anti-V3 and anti-C4 MAbs – reciprocal enhanced binding of some anti-V2 MAbs and anti-CD4 binding site MAbs – binding inhibited by anti-C4 MAbs. Moore & Sodroski [1996]

No. 1300

**MAb ID** K24

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** mouse

**Ab Type** gp120 V3

**Research Contact** Hybridolabs, Institute Pasteur

**References** Altmeyer *et al.* 1999

- K24: A Semliki Forest virus (SFV) expression system carrying BX08 env was used to study the conformation of gp120 env – intracytoplasmic gp120 was recognized by the anti-V3 MAbs K24 and F5.5, while gp120 at the plasma membrane was detected only by conformation dependent MAbs 2G12, 670-D and 694/98D and not V3 MAbs – expression in rat brain also showed that surface-expressed Env was recognized only by the conformation-dependent antibodies and not by anti-V3 antibodies. Altmeyer *et al.* [1999]

No. 1301

**MAb ID** TH1

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L (MN, J)

**Immunogen**

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp120 V3

**Research Contact** Michael Fung, Tanox Biosystem, USA

**References** Gorny & Zolla-Pazner 2004; Yang *et al.* 1998; D'Souza *et al.* 1995

**Keywords** assay development, review, variant cross-recognition or cross-neutralization

- TH1: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. TH1 neutralizes some TCLA strains. Gorny & Zolla-Pazner [2004] (**review**)
- TH1: A neutralization assay was developed based on hemi-nested PCR amplification of the LTR (HNPCR) – LTR-HNPCR consistently revealed HIV DNA and was shown to be a rapid, specific and reliable neutralization assay based on tests with 6 MAbs and 5 isolates. Yang *et al.* [1998] (**assay development**)

- TH1: Found to neutralize MN and JRC5F, but not two B subtype primary isolates, nor a D subtype primary isolate, by most labs in a multi-laboratory study involving 11 labs. D'Souza *et al.* [1995] (**variant cross-recognition or cross-neutralization**)

**No.** 1302

**MAb ID** anti-gp120/V3

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein, virus-like particle (VLP) *Strain:* A clade 94UG018 *HIV component:* Gag, gp120, Nef, Pol

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120 V3

**Research Contact** Intracel Co

**References** Buonaguro *et al.* 2001

- Anti-V3: HIV-1 pr55 gag-based virus-like particles (VLP) carrying Nef and Pol open reading frames as well as gp120 of the clade A isolate 94UG018 were created using a Baculovirus expression system to package additional ORFS into the VLP – anti-V3 and anti-p24 antibodies were used to assess the expression levels and Gag and gp120-TM were found to be expressed at comparable levels on the VLP. Buonaguro *et al.* [2001]

**No.** 1303

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* protein, virus-like particle (VLP) *Strain:* B clade LAI *HIV component:* CD4BS, Gag, V3

**Species (Isotype)** mouse

**Ab Type** gp120 V3

**References** Truong *et al.* 1996

- Antibodies raised against recombinant anti-p55 virus-like particles with the p24 region 196-226 deleted, bearing inserts of either the V3 or the CD4BS regions of gp120 were studied – no neutralizing responses, weak Env, and strong Gag responses were elicited – the major homology region (MHR) and proximal sequences was found to be required for capsid assembly. Truong *et al.* [1996]

**No.** 1304

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** yes

**Immunogen** vaccine

*Vector/Type:* canarypox prime with recombinant protein boost *Strain:* B clade LAI, B clade MN, B clade SF2 *HIV component:* Gag, gp120, gp41, Pol *Adjuvant:* MF59

**Species (Isotype)** human

**Ab Type** gp120 V3

**References** Verrier *et al.* 2000

- Serum Abs elicited by this vaccine reacted with V3 peptides from clades B, C, and F, reacted weakly with V3 peptides from clades A, D, G, and H, and did not react with V3 peptides from clades E and O – neutralizing activity against 5 of 14 primary isolates tested was observed, including one B clade X4 virus, two dualtropic B clade viruses (from clade B) and one clade B and one clade C R5 virus. Verrier *et al.* [2000]

**No.** 1305

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (303–325)

**Epitope**

**Neutralizing** no

**Immunogen** in vitro stimulation or selection

**Species (Isotype)** human (IgM)

**Ab Type** gp120 V3

**References** Sidorova 1999

- Polyspecific anti-MN-24 antibodies were raised through V3 peptide, MN-24 stimulation of human cells, followed by EBV transformation: they react with homologous and heterologous peptides and may be autoantibodies. Sidorova [1999]

**No.** 1306

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**Ab Type** gp120 V3

**References** Guevara *et al.* 2002

- Viral RNA in serum and high titers of subtype C consensus V3 peptide binding Abs were the best independent predictors of mother to infant transmission of HIV-1 subtype C – NAb to subtype B HIV-1 (MN) was also correlated. Guevara *et al.* [2002]

**No.** 1307

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** B

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* HIV-1 captured on concavalin A-immobilized polystyrene nanospheres, Con A-NS *Strain:* B clade IIIB *HIV component:* gp120, heat-inactivated virus *Adjuvant:* concavalin A-immobilized polystyrene nanospheres

**Species (Isotype)** mouse (IgA)

**Ab Type** gp120 V3

**References** Kawamura *et al.* 2002

- Vaginal fluids were collected after intravaginal immunization of BALB/c mice and analyzed for their anti-HIV-1 antibody levels using a IIIB-V3 ELISA and IIIB neutralization assay – HIV-1 specific IgG was undetectable but anti-HIV IgA antibody response was identified in the vaginal fluids of immunized mice with HIV concavalin A-immobilized polystyrene nanospheres. Kawamura *et al.* [2002]

**No.** 1308

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** B

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* B clade 89.6P, B clade MN *HIV component:* Env *Adjuvant:* aluminum hydroxide, Cholera toxin (CT), GM-CSF, IL-12, IL-18, IL-1 $\alpha$

**Species (Isotype)** human (IgA, IgG1, IgG2a)

**Ab Type** gp120 V3

**References** Bradney *et al.* 2002

- The cytokine-adjuvant combination IL-1 $\alpha$ , IL-12 and IL-18 were found to stimulate potent mucosal antibody responses upon intranasal immunization of mice – cholera toxin is the most widely used adjuvant, but is not safe for use in humans. Bradney *et al.* [2002]

**No.** 1309

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Subtype** C

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *Strain:* multiple epitope immunogen *HIV component:* V3 *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse

**Ab Type** gp120 V3

**References** Hewer & Meyer 2002

- A synthetic peptide immunogen designated a multiple epitope immunogen (MEI) was generated by synthesizing peptides with mixtures of frequently found amino acids (>10%) from the C subtypes allowed in the synthetic peptide – when injected into mice, the C subtype MEI induced antibodies that recognized the immunogen and whole virus as an antigen in ELIZAs – sera from eight HIV positive South Africans recognized the MEI peptide in ELISA tests. Hewer & Meyer [2002]

**No.** 1310

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp120 (V3)

**Epitope**

**Subtype** B, C, F

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**Ab Type** gp120 V3

**References** Bongertz *et al.* 2003

**Keywords** rate of progression, subtype comparisons

- Ab responses at dilutions above 1:1000 against the consensus V3 loops of subtypes A, B, C, D, F, and Brazilian B and F, were detected in only 6/60 individuals infected with HIV by sexual exposure, while a significantly higher (38/46) reactivity and frequency of peptide recognition was observed in the plasma of IDUs. High Ab titers (> 1:10,000) were directed against V3B, V3Bbr and V3F peptides. The IDU group also displayed broader NAb responses, in comparison to the sexually transmitted group. This may contribute to a slower disease progression in IDUs. Bongertz *et al.* [2003] (**subtype comparisons, rate of progression**)

**No.** 1311

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** Env

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* adenovirus *Strain:* B clade HXB2/Bal *HIV component:* gp140 $\Delta$ CFI, gp140 $\Delta$ V1V2 $\Delta$ CFI modified V3

**Species (Isotype)** guinea pig (IgG)

**Ab Type** gp120 V3

**References** Yang *et al.* 2004

**Keywords** co-receptor

- Neutralizing antibodies against V3 with greater breadth among B clade viruses were created in vaccinated guinea pigs using a combination gp140 $\Delta$ V1V2 and shortened V3 loop envelope than using intact Envelope. The interior V3 glycosylation site was removed in the modification of V3. This change also caused the virus to become CXCR4 tropic. Yang *et al.* [2004] (**co-receptor**)

**No.** 1312

**MAb ID** 11/75a/21/41

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)**

**Ab Type** gp120 V3 discontinuous

**References** Peet *et al.* 1998; McKeating *et al.* 1992a

- 11/75a/21/41: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, but anti-V3 MAb 11/75a/21/41 binding was dramatically diminished by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and

no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

**No.** 1313  
**MAb ID** 41.1 (ICR41.1i, ICR41. ICR 41.1i)  
**HXB2 Location** Env  
**Author Location** gp120 (HXB10)  
**Epitope**  
**Neutralizing** L (HXB2)  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* gp120  
**Species (Isotype)** rat (IgG2a)  
**Ab Type** gp120 CD4i, gp120 V3 discontinuous  
**Research Contact** J. Cordell, Institute for Cancer Research, Sutton, Surrey, UK  
**References** Heap *et al.* 2005a; Ugolini *et al.* 1997; Jeffs *et al.* 1996; Armstrong *et al.* 1996; Armstrong & Dimmock 1996; McLain & Dimmock 1994; Klasse *et al.* 1993a; McKeating *et al.* 1993b; McKeating *et al.* 1992a; Reitz *et al.* 1988

- 41.1: Called ICR 41.1i. Used as a positive control for enhanced MAb binding after sCD4 exposure – 41.1 binding to virions is increased 2-fold by sCD4. Heap *et al.* [2005a]
- 41.1: Viral binding inhibition by 41.1 was weakly correlated with neutralization (all other neutralizing MAbs tested showed some correlation except 2F5) Ugolini *et al.* [1997]
- 41.1: Called ICR41.1i – IgG2c? – Neutralization was affected if the Ab was added after the virus bound to the host cells at 24 degrees C or below. Armstrong & Dimmock [1996]
- 41.1: Called ICR41.1i – Neutralization occurs by blocking a post-fusion internalization event, in contrast to MAb F58. Armstrong *et al.* [1996]
- 41.1: Deletion of the V1V2 regions did not affect anti-V3 Abs ability to bind when compared to intact rec gp120. Jeffs *et al.* [1996]
- 41.1: Called ICR41.1i – Kinetics of neutralization studied – no lag for 39.3b, while ICR 39.13g and ICR 41.1i have lags of 5 and 15 min respectively – neutralization mediated by 3 molecules of IgG per virion – most efficient at neutralization of the three MAbs studied – acts with multi-hit kinetics. McLain & Dimmock [1994]
- 41.1: The gp41 mutation 582(Ala to Thr) results in conformational changes in gp120 that confer neutralization resistance to conformationally sensitive neutralizing MAbs – neutralization efficiency of 41.1 is not affected. Klasse *et al.* [1993a]; Reitz *et al.* [1988]

**No.** 1314  
**MAb ID** 55/45a/11  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**  
**Ab Type** gp120 V3 discontinuous  
**References** Peet *et al.* 1998

- 55/45a/11: The most variable amino acids in the V3 loop were replaced with serines to make the immunodominant V3 loop less immunogenic – these changes did not affect the ability of sCD4 or MAbs to V1/V2, C1 and C4 to bind, and anti-V3 MAb 55/45a/11 binding was only marginally diminished by V3 serine substitutions – mice injected with serine substituted gp120 had a reduced response relative to wildtype, and no enhanced immunogenicity of conserved regions. Peet *et al.* [1998]

**No.** 1315  
**MAb ID** 1108  
**HXB2 Location** Env  
**Author Location** Env (987)  
**Epitope**  
**Subtype** B  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1λ)  
**Ab Type** gp120 V3 mimotope  
**References** Gorny *et al.* 2004; Gorny & Zolla-Pazner 2004; Zolla-Pazner *et al.* 1999b; Zolla-Pazner *et al.* 1999a  
**Keywords** antibody binding site definition and exposure, antibody generation, mimotopes, review

- 1108: This review provides summaries of Abs that bind to HIV-1 Env. There are many V3 MAbs, many neutralize some TCLA strains, and a subset can also neutralize some primary isolates. Gorny & Zolla-Pazner [2004] (**review**)
- 1108: V3 MAb neutralization is influenced by retaining the epitope, exposure on the intact virion, mobility during CD4-induced conformational change, and affinity. Anti-V3 MAbs selected using V3 peptides neutralize less effectively than V3 MAbs selected using fusion proteins or gp120, suggesting antigenic conformation is important. This MAb was selected using V3 peptides. Gorny *et al.* [2004] (**antibody binding site definition and exposure**)
- 1108: Selected with peptide 987, a mimotope of anti-V3 MAb 447-D – MAb peptide reactivity pattern clustered with immunological related MAbs: 1108, 386, 268, 311, 257, 694.8 – the amino acids HI tended to be critical for reactivity in this group. Zolla-Pazner *et al.* [1999b] (**antibody binding site definition and exposure, antibody generation, mimotopes**)
- 1108: The sequence of peptide 987, used to select MAb 1108, is ADGAWRSVHLGPGRGSGSGMGK. Zolla-Pazner *et al.* [1999a] (**antibody binding site definition and exposure, antibody generation**)

**No.** 1316  
**MAb ID** polyclonal  
**HXB2 Location** Env  
**Author Location** gp120 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *Strain:* B clade MN  
*HIV component:* gp120 *Adjuvant:* Cholera toxin (CT)  
**Species (Isotype)** rabbit

**Ab Type** gp120 V3-C4

**References** Zinckgraf *et al.* 1999

- Nasal mucosal immunization and boosting of HIV peptide and was superior for inducing serum IgG and vaginal secretory IgA compared to nasal immunization and vaginal boosting – vaginal immunization and boosting resulted low serum IgG and vaginal IgA and a high vaginal IgG response. Zinckgraf *et al.* [1999]

**No.** 1317

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgA, IgG)

**Ab Type** gp120 V3, gp120 V4

**References** Skott *et al.* 1999

- IgA and IgG from 45 HIV+ individuals was studied – people with low CD4+ cell counts had decreased levels IgA in saliva – sera and saliva IgA was primarily directed toward Env – peptide ELISA studies indicated that the dominant IgA epitopes were the V4 region (aa 385-409) and the C-term part of the V3 loop (aa 325-344), while the IgG response was directed towards the tip of the loop (aa 308-325). Skott *et al.* [1999]

**No.** 1318

**MAb ID** polyclonal

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Subtype** B

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* peptide *HIV component:* gp41

**Species (Isotype)** rabbit (IgG)

**Ab Type** gp41 alpha-helical hairpin intermediate

**References** Louis *et al.* 2003

**Keywords** vaccine antigen design

- Polyclonal Abs raised against soluble trivalently linked N35CCG-N13 and N34CCG, the internal trimeric core of the coiled-coil ectodomain, inhibit HIV-1 Env-mediated cell fusion at levels comparable to 2G12. Louis *et al.* [2003] (**vaccine antigen design**)

**No.** 1319

**MAb ID** 1367 (1367-D)

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp41 cluster I

**Research Contact** Susan Zolla-Pazner (Zollas01@mccr6.med.nyu) (NYU Med. Center)

**References** Eda *et al.* 2006b; Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Nyambi *et al.* 1998

**Keywords** antibody binding site definition and exposure, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 1367: Called 1367-D. The neutralization potency of this Ab against 7 HIV-1 primary isolates was compared to the neutralization potency of the Ab KD-247. Higher concentrations of 1367-D were needed for the neutralization of all of the HIV-1 isolates suggesting a lower neutralization potency of this Ab. Eda *et al.* [2006b] (**variant cross-recognition or cross-neutralization**)
- 1367: One of 24 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster I region (aa 579 - 604). Only one of these has any neutralizing potential, clone 3. Gorny & Zolla-Pazner [2004] (**review**)
- 1367: A cluster I epitope that binds to rgp41 567-647, recognizes a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41 – this MAb doesn't react with either of the peptides N51 or C43 individually – MAbs 50-69 and 1367 had similar properties. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 1367: Binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 1367: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 5 cluster I anti-gp41 MAbs which showed good cross clade reactivity – 1367 weakly bound to the majority of isolates – no neutralizing activity was observed when tested with 5 isolates, but 1367 did not bind well to these isolates. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1367: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – anti-gp41 Abs 98-6, 1367 and 1342 were not able to bind detectably with any of the viruses from any clade. Nyambi *et al.* [1998] (**subtype comparisons**)

**No.** 1320

**MAb ID** 7B2

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing** no

**Immunogen**

**Species (Isotype)**

**Ab Type** gp41 cluster I

**References** Haynes *et al.* 2005; Binley *et al.* 2003; Binley *et al.* 1999

**Keywords** antibody binding site definition and exposure, vaccine antigen design

- 7B2: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. 7B2 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)
- 7B2: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. gp41 Abs 7B2 and 2.2B did not neutralize in any format, WT, SOS, nor when added postbinding. Binley *et al.* [2003] (**vaccine antigen design**)
- 7B2: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**antibody binding site definition and exposure**)

No. 1321

Mab ID 126-6 (SZ-126.6)

HXB2 Location Env

Author Location gp41 (HXB2)

Epitope

Subtype B

Neutralizing no

Immunogen HIV-1 infection

Species (Isotype) human (IgG2κ)

Ab Type gp41 cluster II

Research Contact Susan Zolla-Pazner (Zollas01@mcr6.med.nyu), NYU Med Center, NY, NY

References Holl *et al.* 2006a; Gorny & Zolla-Pazner 2004; Finnegan *et al.* 2002; Nyambi *et al.* 2000; Gorny & Zolla-Pazner 2000; Hioe *et al.* 1997b; Earl *et al.* 1997; Binley *et al.* 1996; Chen *et al.* 1995; Eddleston *et al.* 1993; Xu *et al.* 1991; Robinson *et al.* 1991; Robinson *et al.* 1990b

**Keywords** antibody binding site definition and exposure, dendritic cells, enhancing activity, kinetics, neutralization, review, subtype comparisons, variant cross-recognition or cross-neutralization

- 126-6: NIH AIDS Research and Reference Reagent Program: 1243.
- 126-6: This Ab did not inhibit HIV-1 BaL replication in macrophages or in PHA-stimulated PBMCs. Holl *et al.* [2006a] (**neutralization, dendritic cells**)
- 126-6: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 126-6: Anti-gp41 MAbs were tested in a cell-cell fusion system to investigate the antigenic changes in gp41 during binding and fusion. Cluster I MAbs 50-69, F240, 240-D, 3D6, and 246-D recognize a nonhelical hydrophobic region, positions 598-604, that forms a disulfide loop in the six-helix bundle. Cluster II MAbs 98-6 and 126-6 recognized residues 644-663 of gp41, a portion of the second heptad repeat. These MAbs were found to behave similarly, so 50-69 and 98-6 were used as representatives. Exposure of cluster I and cluster II epitopes required CD4 expression on HIV HXB2 Env expressing HeLa target cells, but not the CXCR4 co-receptor. Binding to CD4 exposed hidden cluster I and II epitopes. The MAbs were found to bind to gp120/gp41 complexes, not to gp41 after shedding of gp120, and were localized to at fusing-cell interfaces. Kinetic and binding results indicate that these MAbs are exposed in transitional structures during the fusion process, possibly the prehairpin intermediate prior to co-receptor binding, although other intermediate structures may be involved. They do not bind once syncytia begin to show extensive cytoplasmic mixing. These MAbs failed to inhibit fusion. The NAb 2F5 has a very different behavior in this study. Finnegan *et al.* [2002] (**antibody binding site definition and exposure, kinetics**)
- 126-6: This cluster II MAb binds to a conformational epitope in the region 644-663 – like most cluster II MAbs (126-6, 167-D, 1281, 1342, and 1379 all reacted similarly) it binds to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, but not to C43 nor to N51 alone – MAb 126-6 was biotinylated and used as a probe to determine that anti-gp41 MAb 50-69 bound the fusogenic form of the protein in liquid phase. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 126-6: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 cluster II anti-gp41 MAbs – of these 2F5, 167-D, 126-6, and 1281 bound across clades, but usually weakly, while 98-6 and 1342 had poor cross reactivity – Clade D isolates bound most consistently to cluster II MAbs. Nyambi *et al.* [2000] (**variant cross-recognition or cross-neutralization, subtype comparisons**)
- 126-6: Discontinuous epitope recognizing residues between 649-668 – designated cluster II – Fabs D5, D11, G1, T3, M12, M15, S6, S8, S9, S10 block binding. Binley *et al.* [1996] (**antibody binding site definition and exposure**)



- 126-6: One of several anti-gp41 MAbs that bind to a gp41-maltose binding fusion protein designed to study the leucine zipper domain of gp41, showing that the construct has retained aspects of normal gp41 conformation. Chen *et al.* [1995] (**antibody binding site definition and exposure**)
- 126-6: Called SZ-126.6. Eddleston *et al.* [1993]
- 126-6: No enhancing or neutralizing activity. Robinson *et al.* [1991] (**enhancing activity**)
- 126-6: Specific for a conformational epitope. Xu *et al.* [1991] (**antibody binding site definition and exposure**)
- 126-6: No enhancing activity for HIV-1 IIB. Robinson *et al.* [1990b] (**enhancing activity**)

No. 1322

MAb ID 1342

HXB2 Location Env

Author Location gp41

Epitope

Neutralizing no

Immunogen HIV-1 infection

Species (Isotype) human (IgG1 $\lambda$ )

Ab Type gp41 cluster II

Research Contact Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

References Gorny & Zolla-Pazner 2004; Nyambi *et al.* 2000; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Nyambi *et al.* 1998

Keywords antibody binding site definition and exposure, review, subtype comparisons

- 1342: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 1342: This cluster II MAb is a conformational epitope that binds in the region 644-663 – like most cluster II MAbs (126-6, 167-D, 1281, 1342, and 1379 all reacted similarly) it binds to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, but not to C43 nor to N51 alone. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 1342: Binds within the region gp41 647-682 – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)
- 1342: 26 HIV-1 group M isolates (clades A to H) were tested for binding to 47 MAbs, including 6 cluster II anti-gp41 MAbs – of these 2F5, 167-D, 126-6, and 1281 bound across clades, but usually weakly, while 98-6 and 1342 had poor cross reactivity – Clade D isolates bound most consistently to cluster II MAbs – no neutralizing activity was observed when tested with 5 isolates, but 1342 did not bind to these isolates. Nyambi *et al.* [2000] (**subtype comparisons**)
- 1342: Using a whole virion-ELISA method, 18 human MAbs were tested for their ability to bind to a panel of 9 viruses from clades A, B, D, F, G, and H – anti-gp41 Abs 98-6, 1367 and

1342 were not able to bind detectably with any of the viruses from any clade. Nyambi *et al.* [1998] (**subtype comparisons**)

No. 1323

MAb ID 1379

HXB2 Location Env

Author Location gp41

Epitope

Neutralizing

Immunogen HIV-1 infection

Species (Isotype) human (IgG1 $\lambda$ )

Ab Type gp41 cluster II

Research Contact Susan Zolla-Pazner (Zollas01@mcr6.med.nyu) (NYU Med. Center)

References Gorny & Zolla-Pazner 2004; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000

Keywords antibody binding site definition and exposure, review

- 1379: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 1379: This cluster II MAb binds to a conformational epitope in the region 644-663 – like most cluster II MAbs (126-6, 167-D, 1281, 1342, and 1379 all reacted similarly) it binds to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, but not to C43 nor to N51 alone. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 1379: Binds within the region gp41 647-682 – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure**)

No. 1324

MAb ID 2.2B

HXB2 Location Env

Author Location gp41

Epitope

Neutralizing no

Immunogen

Species (Isotype)

Ab Type gp41 cluster II

Research Contact James Robinson, Tulane University, Tulane, LA

References Haynes *et al.* 2005; Binley *et al.* 2003; Schulke *et al.* 2002; Binley *et al.* 1999

Keywords antibody binding site definition and exposure, vaccine antigen design

- 2.2B: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

- 2.2B: The SOS mutant envelope protein introduces a covalent disulfide bond between gp120 surface and gp41 transmembrane proteins into the R5 isolate JR-FL by adding cysteines at residues 501 and 605. Pseudovirions bearing this protein bind to CD4 and co-receptor bearing cells, but do not fuse until treatment with a reducing agent, and are arrested prior to fusion after CD4 and co-receptor engagement. gp41 Abs 7B2 and 2.2B did not neutralize in any format, WT, SOS, nor when added postbinding. Binley *et al.* [2003] (**vaccine antigen design**)
- 2.2B: Ab binding characteristics of SOS gp140 were tested using SPR and RIPA – SOS gp140 is gp120-gp41 bound by a disulfide bond – NAbs 2G12, 2F5, IgG1b12, CD4 inducible 17b, and 19b bound to SOS gp140 better than uncleaved gp140 (gp140unc) and gp120 – non-neutralizing MAbs 2.2B (binds to gp41 in gp140unc) and 23A (binds gp120) did not bind SOS gp140. Schulke *et al.* [2002] (**vaccine antigen design**)
- 2.2B: The MAbs with the broadest neutralizing activity, IgG1b12, 2G12 and 2F5, all have high affinity for the native trimer, indicating that they were raised in an immune response to the oligomer on the virion surface rather than dissociated subunits – a disulfide linked gp120-gp41 (SOS gp140) was created to mimic the native conformation of Env and explore its potential as an immunogen – SOS gp140 is recognized by NAbs IgG1b12, 2G12, and CD4-IgG2, and also by anti-V3 MAbs 19b and 83.1 – SOSgp140 is not recognized by C4 region MAbs that neutralize only TCLA strains, G3-42 and G3-519 – nor did it bind C11, 23A, and M90, MAbs that bind to gp120 C1 and C5, where it interacts with gp41 – MAbs that bind CD4 inducible epitopes, 17b and A32 were very strongly induced by CD4 in SOS gp140 – anti-gp41 MAbs that bind in the region that interacts with gp120, 7B2, 2.2B, T4, T15G1 and 4D4, did not bind to SOSgp140, in contrast to 2F5, which binds to the only gp41 epitope that is well exposed in native gp120-gp41 complexes. Binley *et al.* [1999] (**vaccine antigen design**)

**No.** 1325  
**MAb ID** Fab D11 (D11)  
**HXB2 Location** Env  
**Author Location** gp41 (LAI)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp41 cluster II  
**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996  
**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, review

- Fab D11: Called D11. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab D11: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site**

**definition and exposure, antibody sequence variable domain)**

**No.** 1326  
**MAb ID** Fab D5 (D5)  
**HXB2 Location** Env  
**Author Location** gp41 (LAI)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp41 cluster II  
**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996  
**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, review

- Fab D5: Called D5. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab D5: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody sequence variable domain**)

**No.** 1327  
**MAb ID** Fab G1  
**HXB2 Location** Env  
**Author Location** gp41 (LAI)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)  
**Ab Type** gp41 cluster II  
**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996  
**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, review

- Fab G1: Called G1. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab G1: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody sequence variable domain**)

**No.** 1328  
**MAb ID** Fab M10  
**HXB2 Location** Env  
**Author Location** gp41 (LAI)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster II

**References** Parren *et al.* 1997b; Binley *et al.* 1996

- Fab M10: Does not bind to MN native oligomer, but does bind to both LAI and MN rgp120 and rgp140. Parren *et al.* [1997b]
- Fab M10: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996]

**No.** 1329

**MAB ID** Fab M12 (M12)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster II

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody sequence variable domain, review

- M12 database comment: There is a p15 and a gp120 mouse MAb both called M12 and a human gp41 Fab M12.
- Fab M12: Called M12. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab M12: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody sequence variable domain**)

**No.** 1330

**MAB ID** Fab M15

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster II

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** review

- Fab M15: Called M15. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab M15: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996]

**No.** 1331

**MAB ID** Fab S10 (S10)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster II

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab S10: Called S10. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab S10: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 1332

**MAB ID** Fab S6 (S6)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster II

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain, review

- Fab S6: Called S6. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab S6: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody interactions, antibody sequence variable domain**)

**No.** 1333

**MAB ID** Fab S8 (S8)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster II

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, review

- Fab S8: Called S8. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab S8: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain**)

**No.** 1334

**MAb ID** Fab S9 (S9)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster II

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, review

- Fab S9: Called S9. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab S9: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain**)

**No.** 1335

**MAb ID** Fab T3 (T3)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster II

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab T3: Called T3. One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)

- Fab T3: Binds to cluster II region – competes with MAbs 126-6, Md-1 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 1336

**MAb ID** Md-1 (MD-1)

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing** no

**Immunogen**

**Species (Isotype)** human (IgG1λ)

**Ab Type** gp41 cluster II

**Research Contact** R. A. Myers State of Maryland Dept. of Health

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996; Chen *et al.* 1995; Myers *et al.* 1993

**Keywords** antibody binding site definition and exposure, review

- Md-1: NIH AIDS Research and Reference Reagent Program: 1223.
- Md-1: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Md-1: Discontinuous epitope recognizing residues between 563-672, does not recognize cluster I disulfide bridge region – reacts almost exclusively with trimers and tetramers on WB – designated cluster II – Fabs D5, D11, G1, T3, M12, M15, S6, S8, S9, S10 block binding. Binley *et al.* [1996] (**antibody binding site definition and exposure**)
- Md-1: Called MD-1 – one of several anti-gp41 MAbs that bind to a gp41-maltose binding fusion protein designed to study the leucine zipper domain of gp41, showing that the construct has retained aspects of normal gp41 conformation. Chen *et al.* [1995] (**antibody binding site definition and exposure**)
- Md-1: Called MD-1 – discontinuous epitope that binds in the N-terminal region – reacts exclusively with oligomer. Myers *et al.* [1993] (**antibody binding site definition and exposure**)

**No.** 1337

**MAb ID** Fab A9 (A9)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster III

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab A9: Called A9. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab A9: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 1338

**MAb ID** Fab G15 (G15)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster III

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab G15: Called G15. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab G15: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 1339

**MAb ID** Fab G5

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster III

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab G5: Called G5. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab G5: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 1340

**MAb ID** Fab L1 (L1)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster III

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab L1: Called L1. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab L1: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 1341

**MAb ID** Fab L11 (L11)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster III

**References** Gorny & Zolla-Pazner 2004; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab L11: Called L11. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab L11: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 1342

**MAb ID** Fab L2 (L2)

**HXB2 Location** Env

**Author Location** gp41 (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1κ)

**Ab Type** gp41 cluster III

**Research Contact** P. Perrin and D. Burton (Scripps Research Institute, La Jolla, California)

**References** Gorny & Zolla-Pazner 2004; Earl *et al.* 1997; Binley *et al.* 1996

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, review

- Fab L2: Called L2. One of six Fabs in this database that bind to the gp41 cluster III region (a conformational epitope involving aa 619-648); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- Fab L2: Binds to cluster III region – competes with MAb Md-1, but not MAbs 126-6 and D50 – conformation sensitive – variable regions sequenced. Binley *et al.* [1996] (**antibody binding site definition and exposure, antibody generation, antibody sequence variable domain**)

**No.** 1343

**MAb ID** 1281 (1281-D)

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG1 $\lambda$ )

**Ab Type** gp41 cluster II, gp41six-helix bundle

**Research Contact** Susan Zolla-Pazner (Zollas01@mrcrcr6.med.nyu) (NYU Med. Center)

**References** Gorny & Zolla-Pazner 2004; Follis *et al.* 2002; Golding *et al.* 2002b; Verrier *et al.* 2001; Gorny *et al.* 2000; Gorny & Zolla-Pazner 2000; Hioe *et al.* 1997b

**Keywords** antibody binding site definition and exposure, antibody interactions, review, variant cross-recognition or cross-neutralization

- 1281: One of 19 MAbs and Fabs in this database that bind to the highly immunogenic gp41 cluster II region (aa 644-663); none have neutralizing activity. Gorny & Zolla-Pazner [2004] (**review**)
- 1281: Alanine mutations were introduced into the N- and C-terminal  $\alpha$ -helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 sensitivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- 1281: The fusion process was slowed by using a suboptimal temperature (31.5 C) to re-evaluate the potential of Abs targeting fusion intermediates to block HIV entry – preincubation of E/T cells at 31.5 C enabled polyclonal anti-N-HR Ab and anti-six-helix bundle Abs to inhibit fusion, indicating six-helix bundles form prior to fusion – 98-6 binds to a C-HR hairpin

epitope and blocks fusion when added to a 2 hour E/T preincubation at 31.5 C, but if added after 1 hour, doesn't inhibit – this is in contrast to six-helix bundle Abs 167-D and 1281 that inhibit more efficiently when added after one hour of incubation. Golding *et al.* [2002b] (**antibody binding site definition and exposure**)

- 1281: A panel of 12 MAbs was used to identify those that could neutralize the dual-tropic primary isolate HIV-1 89.6 – six gave significant neutralization at 2 to 10 ug/ml: 2F5, 50-69, IgG1b12, 447-52D, 2G12, and 670-D six did not have neutralizing activity: 654-D, 4.8D, 450-D, 246-D, 98-6, and 1281 – no synergy, only additive effects were seen for pairwise combinations of MAbs, and antagonism was noted between gp41 MAbs 50-69 and 98-6, as well as 98-6 and 2F5. Verrier *et al.* [2001] (**antibody interactions**)
- 1281: This cluster II MAb binds to a conformational epitope in the region 644-663 – like most cluster II MAbs (126-6, 167-D, 1281, 1342, and 1379 all reacted similarly) it binds to a peptide N51-C43 complex trimer of heterodimers that approximates the core of the fusogenic form of gp41, but not to C43 nor to N51 alone. Gorny & Zolla-Pazner [2000] (**antibody binding site definition and exposure**)
- 1281: Binds within the region gp41 647-682 – binding of panel of 21 MAbs to soluble oligomeric gp140 versus gp41 or gp120 monomers was compared – no MAb was oligomer specific, but gp41 MAb 50-69 bound with a 5 fold preference for the oligomer, while other gp41 MAbs (1367, 98-6, 167-D, 1281, 1342, and 1379) did not show a preference. Gorny *et al.* [2000] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization**)
- 1281: Called 1281-D: Four primary isolates showed distinct patterns of sensitivity to neutralization by polyclonal sera and plasma and MAbs – BZ167 was the only isolate inhibited by all polyclonal sera and plasma tested, and was also neutralized by 8/17 MAbs, in particular anti-V3 loop (419-D, 447-52D, 782-D, and 838-D), anti-CD4bd (559/64-D, 654-D and 830-D and a cluster II of gp41 directed MAb (98-6) – isolates 92HT593 and 91US056 were neutralized by V3 loop (419-D, and 447-52D)and cluster II gp41 (98-6) MAbs at higher concentrations – US4 was neutralized by some of the polyclonal sera/plasma tested and not at all by MAbs individually or by a cocktail of ten MAbs consisting of 419-D, 447-52D, 782-D, 838-D, 559/64-D, 654-D, 450-D, 670-D, 1281-D and 98-6. Hioe *et al.* [1997b] (**variant cross-recognition or cross-neutralization**)

**No.** 1344

**MAb ID** Chessie 8

**HXB2 Location** Env

**Author Location** gp41

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** mouse (IgG)

**Ab Type** gp41 cytoplasmic domain

**Research Contact** G. Lewis

**References** Smith-Franklin *et al.* 2002; Rovinski *et al.* 1995; Pombourios *et al.* 1995; Lewis *et al.* 1991

- Chessie 8: This Ab was used in an *in vitro* study demonstrating that HIV-1 antibody and Fcγ receptors can trap virus on the surface of follicular dendritic cells (FDC)'s and extend the period of infectivity – blocking the FDC-Fcγ receptor killing the FDC cell reduced their ability to maintain infectivity, and FDC cells seemed to stabilize viral particles and decrease gp120 shedding. Smith-Franklin *et al.* [2002]
- Chessie 8: Used to precipitate gp160 in immunoblots in a study examining the feasibility of using unprocessed gp160 glycoprotein as an immunogen. Rovinski *et al.* [1995]

No. 1345

**MAb ID** 8F102

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* sCD4-gp120 complex *Strain:*  
B clade HXB2 *HIV component:* gp120

**Species (Isotype)** mouse (IgG)

**Ab Type** gp120-CD4 complex

**References** DeVico *et al.* 1995

- 8F102: MAbs specifically reactive to crosslinked gp120 and CD4 were derived (8F101, 8F102) – conformation dependent – competition studies indicate the epitope is immunogenic in infected humans. DeVico *et al.* [1995]

No. 1346

**MAb ID** CG-10 (CG10)

**HXB2 Location** Env

**Author Location** gp120 (IIIB)

**Epitope**

**Subtype** B

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* sCD4-gp120 complex *Strain:*  
B clade IIIB *HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120-CD4 complex

**Research Contact** Jonathan Gershoni, Tel Aviv University, Israel

**References** Enshell-Seijffers *et al.* 2003; Finnegan *et al.* 2001; Oscherwitz *et al.* 1999a; Sullivan *et al.* 1998b; Rizzuto *et al.* 1998; Lee *et al.* 1997; Wu *et al.* 1996; Gershoni *et al.* 1993

**Keywords** antibody binding site definition and exposure, computational epitope prediction, structure

- CG10: Using 17b MAb to select peptides from a combinatorial library, and analyzing the peptides using a novel discontinuous epitope reconstruction program, enabled epitope prediction. Segments of gp120 were reconstructed as an antigenic protein mimetic recognized by 17b. Comparisons then were made with a similar prediction of contact residues for CG10, a CD4i MAb that competes with 17b, but has a distinct binding site. Enshell-Seijffers *et al.* [2003] (**antibody binding site definition and exposure, computational epitope prediction, structure**)

- CG-10: Called CG10. Using a cell-fusion system, it was found CD4i antibodies 17b, 48d, and CG10 reacted faintly with Env expressing HeLa cells even in the absence of sCD4 or CD4 expressing target cells. Reactivity increased after sCD4 addition, but not after CD4 expressing target cell addition, and binding was not increased at the cell-to-cell CD4-Env interface. This suggests the CD4i co-receptor binding domain is largely blocked at the cell-fusion interface, and so CD4i antibodies would not be able access this site and neutralize cell-mediated viral entry. Finnegan *et al.* [2001] (**antibody binding site definition and exposure**)

- CG-10: Called CG10 – disrupts gp120-CCR5 interaction and competes with MAb 17b – binds near the conserved bridging sheet of gp120 – mutations in positions K/D 121, T/D 123, K/D 207, K/D 421, Q/L 422, Y/S 435, M/A 434, K/A 432 and I/S 423 result in a 70% reduction in CG10 binding. Rizzuto *et al.* [1998]

- CG-10: Called CG10 – CD4BS MAb 15e competes with CG-10 binding, probably due to the disruption of CD4-gp120 by 15e – CD4i MAbs 17b and 48d compete and the binding sites may overlap – MAb A32 enhances binding of 17b, 48d and CG10 – MAbs C11, 2G12 and 212A do not affect CG10 binding – CG-10 can bind gp120 with V1/V2 and V3 deleted – HXBc2 mutations Delta 119-205, 314 G/W, 432 K/A, 183,184 PI/SG decrease CG-10 recognition, HXBc2 mutations Delta 298-327 (V3), 384 Y/E, 298 R/G, 435 Y/S enhance recognition – the CD4 contribution to the CG10 epitope maps to the CD4 CDR2-like loop – CG10 can neutralize HIV-1 in the presence of sCD4 even though it does not do so in the context of cell surface CD4 binding to gp120. Sullivan *et al.* [1998b]

- CG-10: Called CG10 – Promotes envelope mediated cell fusion between CD4+ cells and cells infected with either T-cell and macrophage tropic viruses – infection of HeLa CD4+ (MAGI) cells by HIV-1 LAI, ELI1, and ELI2 strains was increased two-to four-fold in the presence of CG10. Lee *et al.* [1997]

- CG-10: Called CG10 – MIP-1α binding to CCR-5 expressing cells can be inhibited by gp120-sCD4, and MAb CG10 does not block this inhibition. Wu *et al.* [1996]

- CG-10: Reacts exclusively with sCD4-gp120 complex, not with sCD4 or gp120 alone. Gershoni *et al.* [1993]

No. 1347

**MAb ID** CG-25

**HXB2 Location** Env

**Author Location** gp120

**Epitope**

**Neutralizing** L

**Immunogen** vaccine

*Vector/Type:* sCD4-gp120 complex *HIV component:* gp120

**Species (Isotype)** mouse (IgG1)

**Ab Type** gp120-CD4 complex

**References** Gershoni *et al.* 1993

- CG-25: Reacts preferentially with sCD4-gp120, also with sCD4, not with gp120. Gershoni *et al.* [1993]

No. 1348

**MAb ID** CG-4 (CG4)

**HXB2 Location** Env

**Author Location** gp120  
**Epitope**  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *HIV component:* gp120  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120-CD4 complex  
**Research Contact** Jonathan Gershoni, Tel Aviv University, Israel  
**References** Gershoni *et al.* 1993  
 • CG-4: Reacts with gp120 and sCD4-gp120 complex, not with sCD4. Gershoni *et al.* [1993]

**No.** 1349  
**MAb ID** CG-76  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *HIV component:* gp120  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120-CD4 complex  
**References** Gershoni *et al.* 1993  
 • CG-76: Reacts equally well with sCD4-gp120 and sCD4, but not with purified gp120. Gershoni *et al.* [1993]

**No.** 1350  
**MAb ID** CG-9  
**HXB2 Location** Env  
**Author Location** gp120  
**Epitope**  
**Neutralizing** L  
**Immunogen** vaccine  
*Vector/Type:* sCD4-gp120 complex *HIV component:* gp120  
**Species (Isotype)** mouse (IgG1)  
**Ab Type** gp120-CD4 complex  
**References** Gershoni *et al.* 1993  
 • CG-9: Reacts preferentially with sCD4-gp120, also with sCD4, not with gp120. Gershoni *et al.* [1993]

**No.** 1351  
**MAb ID** 105-518  
**HXB2 Location** Env  
**Author Location** gp41 (608–637 HAM112, O group)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* O group HAM112 *HIV component:* gp160  
**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** immunodominant region  
**References** Scheffel *et al.* 1999  
 • 101-518: Overlapping peptides based on group O HAM112 Env were tested for MAb reactivity. Scheffel *et al.* [1999]

**No.** 1352

**MAb ID** 31A1  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing** no  
**Immunogen** in vitro stimulation or selection  
**Species (Isotype)** human (IgMκ/λ)  
**Ab Type** p24+gp41  
**References** Pollock *et al.* 1989  
 • 31A1: Denatured virus was used for *in vitro* stimulation to generate Abs – Reacts with both p24 and gp41. Pollock *et al.* [1989]

**No.** 1353  
**MAb ID** 39A64  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing** no  
**Immunogen** in vitro stimulation or selection  
**Species (Isotype)** human (IgMκ/λ)  
**Ab Type** p24+gp41  
**References** Pollock *et al.* 1989  
 • 39A64: Denatured virus was used for *in vitro* stimulation to generate Abs – Reacts with both p24 and gp41. Pollock *et al.* [1989]

**No.** 1354  
**MAb ID** 39B86  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing** no  
**Immunogen** in vitro stimulation or selection  
**Species (Isotype)** human (IgMκ/λ)  
**Ab Type** p24+gp41  
**References** Pollock *et al.* 1989  
 • 39B86: Denatured virus was used for *in vitro* stimulation to generate Abs – Reacts with both p24 and gp41. Pollock *et al.* [1989]

**No.** 1355  
**MAb ID** 9303  
**HXB2 Location** Env  
**Author Location** gp41  
**Epitope**  
**Neutralizing** no  
**Immunogen**  
**Species (Isotype)** mouse  
**Ab Type** p24+gp41  
**Research Contact** Du Pont  
**References** McDougal *et al.* 1996

**No.** 1356  
**MAb ID** NC-1  
**HXB2 Location** Env  
**Author Location** gp41 (IIIB)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine



*Vector/Type:* peptide *Strain:* B clade IIIB  
*HIV component:* gp41

**Species (Isotype)** mouse (IgG2a)

**Ab Type** gp41 six-helix bundle

**Research Contact** S. Jiang, New York Blood Center, NY, NY

**References** de Rosny *et al.* 2004a; de Rosny *et al.* 2004b; Follis *et al.* 2002; Yang *et al.* 2002; Yang *et al.* 2000; Jiang *et al.* 1998

**Keywords** antibody binding site definition and exposure, antibody generation, antibody interactions, subtype comparisons, variant cross-recognition or cross-neutralization

- NC-1: The MAb 2F5 binds to the C-heptad and is neutralizing, but the MAb D50 binds to the C-heptad and is not neutralizing. 2F5 binds preferentially to native gp41 prior to receptor activation. Trapped fusion-intermediates suggest 2F5 remains present shortly after gp120 triggering by CD4, but may be lost by the time the six-helix bundle is formed. 2F5 neutralization seems to block a later step of the fusion process, but it does not inhibit binding of NC-1, a MAb specific for the six-helix bundle, so it does not prevent formation of the six-helix bundle. The results are most consistent with 2F5 inhibiting a post-fusion-intermediate step. de Rosny *et al.* [2004b] (**antibody binding site definition and exposure, antibody interactions**)
- NC-1: The mechanism of 2F5 neutralization was explored, and experiments suggest it is due to interference with a late step in viral entry. 2F5 does not block six-helix bundle formation, as 2F5 prebinding does not inhibit NC-1 binding, a MAb that binds specifically to the six-helix bundle. de Rosny *et al.* [2004a] (**antibody binding site definition and exposure**)
- NC-1: Alanine mutations were introduced into the N- and C-terminal alpha-helices of gp41 to destabilize interhelical packing interactions in order to study their inhibitory effect on viral infectivity. These mutations were shown to inhibit viral replication though affecting the conformational transition to the fusion-active form of gp41, and allow increased inhibition by gp41 peptides. 2F5 sensitivity is increased in the mutated viruses, presumably because 2F5s neutralization activity is focused on the transition to the fusion active state. No other gp41 MAb against tested, including NC-1, 50-69D, 1281, 98-6D, 246-D and F240, neutralized the parental or the fusion-deficient mutated viruses. Follis *et al.* [2002] (**antibody binding site definition and exposure**)
- NC-1: Uncleaved soluble gp140 can be stabilized in an oligomer by fusion with a C-term trimeric GCN4 motif (gp140delta683(-/GCN4)) or using a T4 trimeric motif derived from T4 bacteriophage fibritin (gp140delta683(-/FT)) – NC-1 binds to 15% of the GCN4 motif trimers, but this was significantly reduced for the T4 fibritin stabilized structures, indicating little is in the six-helix bundle, fusogenic conformation. Yang *et al.* [2002] (**antibody binding site definition and exposure**)
- NC-1: A combination of gp41 fusion with the GNC4 trimeric sequences and disruption of the YU2 gp120-gp41 cleavage site resulted in stable gp140 trimers (gp140-GNC4) – approximately 16% of the gp140(-GNC4) stabilized trimer recognized by pooled sera was precipitated by NC-1, indicating that

at a fraction assumes a fusogenic gp41 six-helix bundle conformation – gp140(-) monomers were not able to bind to the NC-1, nor was gp130(-/GCN4) glycoprotein, consistent with the expectation that the absence of C34 helices would preclude formation of the six-helix bundle. Yang *et al.* [2000] (**antibody binding site definition and exposure**)

- NC-1: Ab elicited in response to immunization with N36(L6)C34, a peptide that folds into a six helix bundle like gp41 – NC-1 binds to the surface of HIV-1 infected cells only in the presence of sCD4, recognizing the fusogenic core structure – binding affinity was decreased by point mutations that disrupt core formation and abolish membrane fusion activity, (I573P and I573A) – NC-1 can recognize discontinuous epitopes from B clade isolate SC, but not E clade strain N243, O group strain GAB, or HIV-2 ROD. Jiang *et al.* [1998] (**antibody binding site definition and exposure, antibody generation, variant cross-recognition or cross-neutralization, subtype comparisons**)

#### IV-C-18 Nef Antibodies

**No.** 1357

**MAb ID** 4H4

**HXB2 Location** Nef (1–33)

**Author Location** Nef (1–33 IIIB)

**Epitope** MGGKWSKSSVVGWPTVRERMRRAPTVRERMRRAEPAADGVGAA

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade IIIB

*HIV component:* Nef

**Species (Isotype)** human (IgG1)

**References** Otake *et al.* 1994

- 4H4: This MAb, elicited by vaccination with a Nef fusion protein, could not detect Nef protein on the cell surface – C-term anti-Nef Abs could. Otake *et al.* [1994]

**No.** 1358

**MAb ID** polyclonal

**HXB2 Location** Nef (9–24)

**Author Location** Nef (9–24)

**Epitope** SVIGWLTVRERMRRAE

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* DNA *Strain:* B clade BRU

*HIV component:* Nef

**Species (Isotype)** mouse (IgG)

**References** Tahtinen *et al.* 2001

- BALB/c mice were immunized with a pBN-vector expressing HIV-1 nef, rev, or tat genes – DNA loaded onto gold microparticles was delivered using a gene gun, and DNA dissolved in saline was given intradermally or intramuscularly – Nef gene gun immunized mice showed the strongest and most long-lasting (6 months) Ab, CTL and proliferative responses – the highest IgG1/IgG2a ratio was observed in the gene gun immunized mice – three Ab binding sites were found in Nef using peptide mapping, although some sera reacted only to

complete Nef – Rev- or-Tat immunized mice did not generate an Ab response. Tahtinen *et al.* [2001]

**No.** 1359  
**MAb ID** 13/042  
**HXB2 Location** Nef (11–20)  
**Author Location** Nef (11–24 BH10)  
**Epitope** VGWPTVRERM  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
**Species (Isotype)** mouse  
**References** Schneider *et al.* 1991  
 • 13/042: Epitope mapped by overlapping decapeptides – core: TVRERM. Schneider *et al.* [1991]

**No.** 1360  
**MAb ID** 13/035  
**HXB2 Location** Nef (15–24)  
**Author Location** Nef (11–24 BH10)  
**Epitope** TVRERMRAE  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
**Species (Isotype)** mouse  
**References** Schneider *et al.* 1991  
 • 13/035: Epitope mapped by overlapping decapeptides – core: TVRERM. Schneider *et al.* [1991]

**No.** 1361  
**MAb ID** A6  
**HXB2 Location** Nef (18–26)  
**Author Location** Nef (18–26 NL-432)  
**Epitope** ERMRAEPA?  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse (IgM)  
**References** Otake *et al.* 1997  
**Keywords** antibody binding site definition and exposure, antibody generation  
 • A6: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. A6 bound to the peptide spanning amino acids 18-26; we inferred the amino acids from the positions in the NL-43 strain. A6 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure, antibody generation**)

**No.** 1362  
**MAb ID** AM5C6  
**HXB2 Location** Nef (28–43)  
**Author Location** Nef (28–43 BH10)  
**Epitope** DGVGAASRDLEKHGAI+KAAVDLSHFLK  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
**Species (Isotype)** mouse  
**References** Maksutov *et al.* 2002; Schneider *et al.* 1991

• AM5C6: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksutov *et al.* [2002]  
 • AM5C6: Epitope mapped by overlapping decapeptides – core: SRDL – also reacts with Nef(78-92). Schneider *et al.* [1991]

**No.** 1363  
**MAb ID** AM5C6  
**HXB2 Location** Nef (28–43)  
**Author Location** Nef (28–43 BH10)  
**Epitope** DGVGAASRDLEKHGAI+KAAVDLSHFLK  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
**Species (Isotype)** mouse

**References** Maksutov *et al.* 2002; Schneider *et al.* 1991  
 • AM5C6: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksutov *et al.* [2002]  
 • AM5C6: Epitope mapped by overlapping decapeptides – core: KAAVDL – also reacts with Nef(28-43). Schneider *et al.* [1991]

**No.** 1364  
**MAb ID** A7  
**HXB2 Location** Nef (28–45)  
**Author Location** Nef (28–45 NL-432)  
**Epitope** DGVGAASRDLEKHGAI?  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse (IgG1)  
**References** Otake *et al.* 1997  
**Keywords** antibody binding site definition and exposure, antibody generation

• A7: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. A7 bound to the peptide spanning amino acids 28-45; we inferred the amino acids from the positions in the NL-43 strain. A7 did not bind to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure, antibody generation**)

**No.** 1365  
**MAb ID** 25/03  
**HXB2 Location** Nef (30–43)  
**Author Location** Nef (30–43 BH10)  
**Epitope** VGAASRDLEKHGAI  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
**Species (Isotype)** mouse

**References** Maksutov *et al.* 2002; Schneider *et al.* 1991  
 • 25/03: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksutov *et al.* [2002]  
 • 25/03: Epitope mapped by overlapping decapeptides – core: ASRDLEK. Schneider *et al.* [1991]

**No.** 1366  
**MAb ID** 26/76  
**HXB2 Location** Nef (30–43)  
**Author Location** Nef (30–43 BH10)  
**Epitope** VGAASRDLEKHGAI  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
**Species (Isotype)** mouse  
**References** Maksiutov *et al.* 2002; Schneider *et al.* 1991  
 • 26/76: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]  
 • 26/76: Epitope mapped by overlapping decapeptides – core: SRDLEK. Schneider *et al.* [1991]

**No.** 1367  
**MAb ID** 3F2  
**HXB2 Location** Nef (31–40)  
**Author Location** Nef (31–40 BRU)  
**Epitope** GAASRDLEKH  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Nef  
**Species (Isotype)** mouse (IgG1)  
**References** Maksiutov *et al.* 2002; Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992  
 • 3F2: UK Medical Research Council AIDS reagent: EVA3067.1.  
 • 3F2: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]  
 • 3F2: Faintly cross-reactive with astrocytes of uninfected control samples. Ranki *et al.* [1995]  
 • 3F2: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

**No.** 1368  
**MAb ID** 3D12  
**HXB2 Location** Nef (31–50)  
**Author Location** Nef (31–50 BRU)  
**Epitope** GAASRDLEKHGAISSNTAA  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Nef  
**Species (Isotype)** mouse (IgG1)  
**References** Maksiutov *et al.* 2002; Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992  
 • 3D12 database comment: There is an anti-RT MAb that also has this name.  
 • 3D12: UK Medical Research Council AIDS reagent: EVA3067.2.  
 • 3D12: This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]

• 3D12: One of four antibodies used in combination to show HIV Nef protein expressed in astrocytes from 7/14 brain samples from HIV+ individuals – Nef expression associated with dementia. Ranki *et al.* [1995]  
 • 3D12: Over-expression of Nef in astrocytes from postmortem pediatric CNS tissues. Saito *et al.* [1994]  
 • 3D12: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

**No.** 1369  
**MAb ID** polyclonal  
**HXB2 Location** Nef (33–65)  
**Author Location** Nef (32–64 LAI, BRU)  
**Epitope** ASRDLEKHGAISSNTAATNAACAWLEAQEEEE  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* protein, PLG microparticle  
*Strain:* B clade BRU, B clade LAI *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA), PLG  
**Species (Isotype)** mouse (IgG1)  
**References** Maksiutov *et al.* 2002; Moureau *et al.* 2002  
 • This epitope is similar to a fragment of the human protein vascular endothelial growth factor C, AEPDAGEATAYASKDLE. Maksiutov *et al.* [2002]  
 • Nef encapsulated in poly(DL-lactide-co-glycolide) (PLG) had a more prolonged Ab response than Nef in PBS or in Freund's adjuvant (CFA), still strong after 7 months – the response was predominantly IgG1, a Th2 immune response – three linear epitopes, Nef 32-64, 118-167, and 185-205, were frequently recognized by the sera of mice immunized with NefPLG or Nef-CFA, but not after immunization with Nef in PBS, which seemed to preferentially stimulate an Ab response to conformational epitopes. Moureau *et al.* [2002]

**No.** 1370  
**MAb ID** polyclonal  
**HXB2 Location** Nef (49–64)  
**Author Location** Nef (49–64)  
**Epitope** AATNAACAWLEAQEEE  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade BRU  
*HIV component:* Nef  
**Species (Isotype)** mouse (IgG)  
**References** Tahtinen *et al.* 2001  
 • BALB/c mice were immunized with a pBN-vector expressing HIV-1 nef, rev, or tat genes – DNA loaded onto gold microparticles was delivered using a gene gun, and DNA dissolved in saline was given intradermally or intramuscularly – Nef gene gun immunized mice showed the strongest and most long-lasting (6 months) Ab, CTL and proliferative responses – the highest IgG1/IgG2a ratio was observed in the gene gun immunized mice – three Ab binding sites were found in Nef using peptide mapping, although some sera reacted only to complete Nef – Rev- or-Tat immunized mice did not generate an Ab response. Tahtinen *et al.* [2001]

**No.** 1371

**MAb ID** 3G12  
**HXB2 Location** Nef (51–71)  
**Author Location** Nef (51–71 BRU)  
**Epitope** TNAACAWLEAQEEEEVGFPVT  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Nef  
**Species (Isotype)** mouse (IgG2a)  
**References** Ovod *et al.* 1992  
 • 3G12: Reacted with Nef from different HIV-1 strains (BRU, IIIIB, RF, MN). Ovod *et al.* [1992]

**No.** 1372  
**MAb ID** 13/058  
**HXB2 Location** Nef (60–73)  
**Author Location** Nef (60–73 BH10)  
**Epitope** AQEEEEVGFPVTPQ  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
**Species (Isotype)** mouse  
**References** Schneider *et al.* 1991  
 • 13/058: Epitope mapped by overlapping decapeptides – core: EEVGFP. Schneider *et al.* [1991]

**No.** 1373  
**MAb ID** 26/028  
**HXB2 Location** Nef (60–73)  
**Author Location** Nef (60–73 BH10)  
**Epitope** AQEEEEVGFPVTPQ  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
**Species (Isotype)** mouse  
**References** Schneider *et al.* 1991  
 • 26/028: Epitope mapped by overlapping decapeptides – core: EEVGFPV. Schneider *et al.* [1991]

**No.** 1374  
**MAb ID** polyclonal  
**HXB2 Location** Nef (61–71)  
**Author Location** Nef  
**Epitope** QEEEEVGFPVT  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* Env, Gag, Nef, Pol  
**Species (Isotype)** rabbit  
**References** Li *et al.* 2005  
**Keywords** mimics  
 • In early HIV-1 infection, patients develop autoimmune thrombocytopenia, with Ab directed against beta3 integrin, GPIIIa49-66. Panning with a 7-mer phage display library using rabbit anti-GPIIIa49-66 (CAPESIEFPVSEARVLED), the immunodominant epitope of the identified potential molecular mimicry epitopes with HIV-1 Env (sklFDeGLFn, elfnk-TIIFP), Pol (geAPEFPskq), Gag (gktHyMINPl) and Nef (qeeeeVgFPVt, qeeeeVgFPVt, edeGigFPVr, fkLVPVSEae, ssnTPPTNaa) proteins. Pools of these peptides elicited Ab in

rabbits that induce platelet oxidation in vitro and thrombocytopenia in vivo upon passive transfer. Nef (qeeeeVgFPVt), Gag (gktHyMINPl), and Nef (fkLVPVSEae) all overlap with known HIV-1 epitopes. Li *et al.* [2005] (**mimics**)

**No.** 1375  
**MAb ID** 2E3  
**HXB2 Location** Nef (61–80)  
**Author Location** Nef (61–80 BRU)  
**Epitope** QEEEEVGFPVTPQVPLRPMT  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Nef  
**Species (Isotype)** mouse (IgG1)  
**References** Nilsen *et al.* 1996; Ovod *et al.* 1992  
 • 2E3: There are two MAbs with the name 2E3 – the other one binds to integrase. Nilsen *et al.* [1996]  
 • 2E3: Two isomorphous forms of Nef were identified, 2E3 reacted with the p24 but not p27 form, and was strain specific (MN and BRU reactive, not IIIIB or RF). Ovod *et al.* [1992]

**No.** 1376  
**MAb ID** polyclonal  
**HXB2 Location** Nef (66–97)  
**Author Location** Nef (66–97 LAI)  
**Epitope** VGFPVTPQVPLRPMTYKAAVDLSHFLKEKGG  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Nef *Adjuvant:* QS21  
**Species (Isotype)** human (IgG)  
**References** Pialoux *et al.* 2001  
 • 28 subjects were vaccinated with six HIV-1 peptides that were selected to be particularly rich in CTL epitopes, presented in lipopeptides with or without adjuvant QS21 – HIV-specific Ab responses were detected in 10/28, proliferative in 11/14, and CTL in 13/24 (54%) of testable volunteers – 10/28 had Ab responses to this peptide (N1), 11/24 had proliferative responses, and CTL responses were detected. Pialoux *et al.* [2001]

**No.** 1377  
**MAb ID** F14.11  
**HXB2 Location** Nef (83–88)  
**Author Location** Nef (83–88)  
**Epitope** AAVDLS  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* Nef  
**Species (Isotype)** mouse (IgG2ak)  
**References** Chang *et al.* 1998; De Santis *et al.* 1991  
 • F14.11: Used as a control in a study of Nef-specific single chain Abs constructed from AG11 and EH1. Chang *et al.* [1998]  
 • F14.11: The MAb was made to a six aa region of Nef that is similar to a region found in thymosin alpha 1 protein – the MAb binds to the natural Nef protein. De Santis *et al.* [1991]

**No.** 1378  
**MAb ID** 31/03  
**HXB2 Location** Nef (83–103)  
**Author Location** Nef (82–103 BH10)  
**Epitope** AAVDLSHFLKEKGGLEGLIHS  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
**Species (Isotype)** mouse  
**References** Schneider *et al.* 1991  
 • 31/03: Epitope mapped by overlapping decapeptides – mapping suggests complex epitope in this region. Schneider *et al.* [1991]

**No.** 1379  
**MAb ID** polyclonal  
**HXB2 Location** Nef (90–98)  
**Author Location** Nef (NL43)  
**Epitope** FLKEKGGLE  
**Neutralizing**  
**Immunogen** HIV-1 infection, vaccine  
**Species (Isotype)** human, rabbit  
**References** Yamada & Iwamoto 1999  
**Keywords** ADCC, antibody binding site definition and exposure, antibody generation, complement, rate of progression  
 • Antibody responses to overlapping 9-mers from the Nef protein were mapped in a set of HIV+ Japanese hemophiliacs. Long term non-progressors among the group were significantly more likely to react to Nef peptide 31 (FLKEKGGLE) ( $p=0.008$ ). Rabbit polyclonal Abs were raised against this peptide. These Abs bound Nef, could kill infected cells in a complement dependent manner, and the domain near peptide 31 was exposed on the surface of infected T-cells. Yamada & Iwamoto [1999] (**ADCC, antibody binding site definition and exposure, antibody generation, complement, rate of progression**)

**No.** 1380  
**MAb ID** polyclonal  
**HXB2 Location** Nef (90–98)  
**Author Location** Nef  
**Epitope** FLKEKGGLE  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Yamada *et al.* 2004  
**Keywords** ADCC, rate of progression  
 • Plasma and PBMC from long term non-progressors can mediate ADCC against Nef infected target cells. Addition of the peptide FLKEKGGLE reduces this activity by half. Patients who were LTNP were found to make antibodies against this peptide in an earlier study. Anti-Gag antibodies do not elicit ADCC, and Pol proteins are not expressed on the cell surface, in contrast to this Nef epitope. Yamada *et al.* [2004] (**ADCC, rate of progression**)

**No.** 1381  
**MAb ID** F4  
**HXB2 Location** Nef (115–126)

**Author Location** Nef (115–126 NL-432)  
**Epitope** YHTQGYFPDWQN?  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* Nef  
**Species (Isotype)** mouse (IgG1)  
**References** Otake *et al.* 1997  
**Keywords** antibody binding site definition and exposure, antibody generation  
 • F4: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. F4 bound to the peptide spanning amino acids 115–126; we inferred the amino acids from the positions in the NL-43 strain. A6 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure, antibody generation**)

**No.** 1382  
**MAb ID** F2  
**HXB2 Location** Nef (115–136)  
**Author Location** Nef (115–137 NL-432)  
**Epitope** YHTQGYFPDWQNYTPGGVRYYP?  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (Isotype)** mouse (IgG1)  
**References** Otake *et al.* 1997  
**Keywords** antibody binding site definition and exposure, antibody generation  
 • F2: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. F2 bound to the peptide spanning amino acids 115–137; we inferred the amino acids from the positions in the NL-43 strain. F2 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure, antibody generation**)

**No.** 1383  
**MAb ID** polyclonal  
**HXB2 Location** Nef (117–147)  
**Author Location** Nef (117–147 LAI)  
**Epitope** TQGYFPDWQNYTPGGVRYPLTFGWYKLVLP  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* lipopeptide *Strain:* B clade LAI *HIV component:* Nef *Adjuvant:* QS21  
**Species (Isotype)** human (IgG)  
**References** Pialoux *et al.* 2001  
 • 28 subjects were vaccinated with six HIV-1 peptides that were selected to be particularly rich in CTL epitopes, presented in lipopeptides with or without adjuvant QS21 – HIV-specific Ab responses were detected in 25/28, proliferative in 3/24, and CTL in 13/24 (54%) of testable volunteers – 20/28 had antibody responses to this particular peptide (N2), 3/24 had proliferative responses, and CTL responses were detected. Pialoux *et al.* [2001]

**No.** 1384  
**MAb ID** polyclonal  
**HXB2 Location** Nef (118–133)  
**Author Location** Nef (118–133)  
**Epitope** QGYFPDWQNYTPGGPV  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* DNA *Strain:* B clade BRU  
*HIV component:* Nef  
**Species (Isotype)** mouse (IgG)  
**References** Tahtinen *et al.* 2001

- BALB/c mice were immunized with a pBN-vector expressing HIV-1 nef, rev, or tat genes—DNA loaded onto gold microparticles was delivered using a gene gun, and DNA dissolved in saline was given intradermally or intramuscularly—Nef gene gun immunized mice showed the strongest and most long-lasting (6 months) Ab, CTL and proliferative responses—the highest IgG1/IgG2a ratio was observed in the gene gun immunized mice—three Ab binding sites were found in Nef using peptide mapping, although some sera reacted only to complete Nef—Rev- or Tat-immunized mice did not generate an Ab response. Tahtinen *et al.* [2001]

**No.** 1385  
**MAb ID** polyclonal  
**HXB2 Location** Nef (119–168)  
**Author Location** Nef (118–167 LAI, BRU)  
**Epitope** GYFPDWQNYTPGGVRYPLTFGWCYKLVPEP-DKVEEANKGENTSLHPV  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection, vaccine  
*Vector/Type:* protein, PLG microparticle  
*Strain:* B clade BRU, B clade LAI *HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA), PLG  
**Species (Isotype)** mouse (IgG1)  
**References** Maksutov *et al.* 2002; Moureau *et al.* 2002

- This epitope is similar to a fragment of the human protein Bone-derived growth factor, PLEPAKLEE, and to Hematopoietic progenitor cell antigen CD34, TSLHPVSQHG. Maksutov *et al.* [2002]
- Nef encapsulated in poly(DL-lactide-co-glycolide) (PLG) had a more prolonged Ab response than Nef in PBS or in Freund's adjuvant (CFA), still strong after 7 months – the response was predominantly IgG1, a Th2 immune response – three linear epitopes, Nef 32-64, 118-167, and 185-205, were frequently recognized by the sera of mice immunized with NefPLG or Nef-CFA, but not after immunization with Nef in PBS, which seemed to preferentially stimulate an Ab response to conformational epitopes. Moureau *et al.* [2002]

**No.** 1386  
**MAb ID** F3  
**HXB2 Location** Nef (128–137)  
**Author Location** Nef (128–137 NL-432)  
**Epitope** TPGPGVRYPL?  
**Neutralizing**  
**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (Isotype)** mouse (IgG1)  
**References** Kawai *et al.* 2003; Otake *et al.* 1997  
**Keywords** antibody binding site definition and exposure, antibody generation, complement

- F3: Used as a control for Nef binding in a study designed to elicit anti-Nef IgM human Abs in trans-chromosome mice that carry human chromosomes responsible for Ig production. These mice were immunized with recombinant Nef protein. Human heavy chain, mouse light chain anti-Nef IgM were obtained. The hope was that these human IgM anti-Nef chimeric Abs would activate complement mediated cytolysis; C3 deposition was induced but not at high enough levels to induce lysis. Kawai *et al.* [2003] (**complement**)
- F3: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. F3 bound to the peptide spanning amino acids 128-137; we inferred the amino acids from the positions in the NL-43 strain. F3 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure, antibody generation**)

**No.** 1387  
**MAb ID** F8  
**HXB2 Location** Nef (128–137)  
**Author Location** Nef (128–137 NL-432)  
**Epitope** TPGPGVRYPL?  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (Isotype)** mouse (IgM)  
**References** Otake *et al.* 1997  
**Keywords** antibody binding site definition and exposure, antibody generation

- F8: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. F8 bound to the peptide spanning amino acids 128-137; we inferred the amino acids from the positions in the NL-43 strain. F8 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure, antibody generation**)

**No.** 1388  
**MAb ID** polyclonal  
**HXB2 Location** Nef (143–151)  
**Author Location** Nef  
**Epitope** FKLVPVSEAE  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* peptide *HIV component:* Env, Gag, Nef, Pol  
**Species (Isotype)** rabbit  
**References** Li *et al.* 2005  
**Keywords** mimics

- In early HIV-1 infection, patients develop autoimmune thrombocytopenia, with Ab directed against beta3 integrin, GPIIIa49-66. Panning with a 7-mer phage display library using rabbit anti-GPIIIa49-66 (CAPESIEFPVSEARVLED), the immunodominant epitope of the identified potential molecular mimicry epitopes with HIV-1 Env (skIFDeGLFn, elfnk-TIIFP), Pol (geAPEFPskq), Gag (gktHyMINPI) and Nef (qeeeeVgFPVt, qeeeeVgFPVt, edeGigFPVr, fklVPVSEae, ssnTPPTNaa) proteins. Pools of these peptides elicited Ab in rabbits that induce platelet oxidation in vitro and thrombocytopenia in vivo upon passive transfer. Nef (qeeeeVgFPVt), Gag (gktHyMINPI), and Nef (fklVPVSEae) all overlap with known HIV-1 epitopes. Li *et al.* [2005] (**mimics**)

**No.** 1389

**MAb ID** F1

**HXB2 Location** Nef (148–157)

**Author Location** Nef (148–157 IIIB)

**Epitope** VEPDKVEEAN

**Neutralizing**

**Immunogen**

**Species (Isotype)** mouse (IgM)

**References** Haynes *et al.* 2005; Fujii *et al.* 1996b; Fujii *et al.* 1996c; Otake *et al.* 1994; Fujii *et al.* 1993

- F1: There is a Nef (Fujii1993) and a CD4BS (Haynes2005) MAb that are called F1. Fujii *et al.* [1993]; Haynes *et al.* [2005]
- F1: Insect cells expressing myristylated Nef proteins on their cell surface can induce cytolysis of unstimulated CD4+ cells – this response is not due to MHC restricted CTL activity – the cell surface of Nef expressing insect cells carry Nef that can be recognized by MAbs E7 and E9 but not F1. Fujii *et al.* [1996c]
- F1: A carboxy-terminal domain of Nef on the cell surface induces cytolysis of CD4+ T cells. Fujii *et al.* [1996b]
- F1: The C-term end of Nef is accessible to Abs at the cell surface – stained IIIB/M10, but not MN/M10, cells. Fujii *et al.* [1993]; Otake *et al.* [1994]

**No.** 1390

**MAb ID** 2F2

**HXB2 Location** Nef (151–170)

**Author Location** Nef (151–170 BRU)

**Epitope** DKVEEANKGENTSLHPVSL

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *HIV component:* Nef

**Species (Isotype)** mouse (IgG1)

**References** Maksutov *et al.* 2002; Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992

- 2F2: UK Medical Research Council AIDS reagent: EVA3067.3.
- 2F2: This epitope is similar to a fragment of the human protein Hematopoietic progenitor cell antigen CD34, TSLH-PVSQHG. Maksutov *et al.* [2002]
- 2F2: One of four antibodies used in combination to show HIV Nef protein expressed in astrocytes from 7/14 brain samples from HIV+ individuals – Nef expression associated with dementia. Ranki *et al.* [1995]

- 2F2: Over-expression of Nef in astrocytes from postmortem pediatric CNS tissue. Saito *et al.* [1994]
- 2F2: Strain specific (MN and BRU reactive, not IIIB or RF). Ovod *et al.* [1992]

**No.** 1391

**MAb ID** E9

**HXB2 Location** Nef (158–181)

**Author Location** Nef (158–206 IIIB)

**Epitope** KGENTSLHPVSLHGMDDPEREVL

**Neutralizing**

**Immunogen**

**Species (Isotype)** mouse (IgM)

**References** Maksutov *et al.* 2002; Fujii *et al.* 1996b; Fujii *et al.* 1996c; Otake *et al.* 1994; Fujii *et al.* 1993

- E9: This epitope is similar to a fragment of the human protein Hematopoietic progenitor cell antigen CD34, TSLH-PVSQHG. Maksutov *et al.* [2002]
- E9: A carboxy-terminal domain of Nef on the cell surface induces cytolysis of CD4+ T cells. Fujii *et al.* [1996b]
- E9: Insect cells expressing myristylated Nef proteins on their cell surface can induce cytolysis of unstimulated CD4+ cells – this response is not due to MHC restricted CTL activity – the cell surface of Nef expressing insect cells carry Nef that can be recognized by MAbs E7 and E9 but not F1. Fujii *et al.* [1996c]
- E9: The C-term end of Nef is accessible to Abs at the cell surface – stained IIIB/M10, but not MN/M10, cells. Fujii *et al.* [1993]; Otake *et al.* [1994]

**No.** 1392

**MAb ID** 3E6

**HXB2 Location** Nef (161–180)

**Author Location** Nef (161–180 BRU)

**Epitope** NTSLLHPVSLHGMDDPEREV

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BRU

*HIV component:* Nef

**Species (Isotype)** mouse (IgG1)

**References** Maksutov *et al.* 2002; Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992

- 3E6: UK Medical Research Council AIDS reagent: EVA3067.4.
- 3E6: This epitope is similar to a fragment of the human protein Hematopoietic progenitor cell antigen CD34, TSLH-PVSQHG. Maksutov *et al.* [2002]
- 3E6: Faintly cross-reactive with astrocytes of uninfected control samples. Ranki *et al.* [1995]
- 3E6: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

**No.** 1393

**MAb ID** E5

**HXB2 Location** Nef (170–181)

**Author Location** Nef (170–181)

**Epitope** LHGMDDPEREVL?

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade NL43  
*HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA)

**Species (Isotype)** mouse (IgM)

**References** Otake *et al.* 1997

**Keywords** antibody binding site definition and exposure, antibody generation

- E5: BALB/c mice were immunized with Nef protein to create a series of anti-Nef antibodies. E5 bound to the peptide spanning amino acids 170-181; we inferred the amino acids from the positions in the NL-43 strain. E5 also bound to the complete Nef protein. Otake *et al.* [1997] (**antibody binding site definition and exposure, antibody generation**)

**No.** 1394

**MAb ID** 2A3

**HXB2 Location** Nef (171–190)

**Author Location** Nef (171–190 BRU)

**Epitope** HGMDDPEREVLEWRFSRLA

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Nef

**Species (Isotype)** mouse (IgG1)

**References** Ovod *et al.* 1992

- 2A3: Reacted with Nef from different HIV-1 strains (BRU, IIIB, MN, but not RF). Ovod *et al.* [1992]

**No.** 1395

**MAb ID** 2E4

**HXB2 Location** Nef (171–190)

**Author Location** Nef (171–190 BRU)

**Epitope** HGMDDPEREVLEWRFSRLA

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Nef

**Species (Isotype)** mouse (IgG1)

**References** Ovod *et al.* 1992

- 2E4: Reacted with Nef from different HIV-1 strains (BRU, IIIB, MN but not RF). Ovod *et al.* [1992]

**No.** 1396

**MAb ID** 2H12

**HXB2 Location** Nef (171–190)

**Author Location** Nef (171–190 BRU)

**Epitope** HGMDDPEREVLEWRFSRLA

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Nef

**Species (Isotype)** mouse (IgG1)

**References** Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992

- 2H12: One of four antibodies used in combination to show HIV Nef protein expressed in astrocytes from 7/14 brain samples from HIV+ individuals – Nef expression associated with dementia. Ranki *et al.* [1995]
- 2H12: Over-expression of Nef in astrocytes from postmortem pediatric CNS tissue. Saito *et al.* [1994]

- 2H12: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

**No.** 1397

**MAb ID** 3A2

**HXB2 Location** Nef (171–190)

**Author Location** Nef (171–190 BRU)

**Epitope** HGMDDPEREVLEWRFSRLA

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* protein *Strain:* B clade BRU  
*HIV component:* Nef

**Species (Isotype)** mouse (IgG1)

**References** Ranki *et al.* 1995; Saito *et al.* 1994; Ovod *et al.* 1992

- 3A2: UK Medical Research Council AIDS reagent: EVA3067.5.
- 3A2: One of four antibodies used in combination to show HIV Nef protein expressed in astrocytes from 7/14 brain samples from HIV+ individuals – Nef expression associated with dementia. Ranki *et al.* [1995]
- 3A2: Over-expression of Nef in astrocytes from postmortem pediatric CNS tissue. Saito *et al.* [1994]
- 3A2: Reacted with Nef from different HIV-1 strains (BRU, IIIB, RF, MN). Ovod *et al.* [1992]

**No.** 1398

**MAb ID** NF1A1

**HXB2 Location** Nef (173–206)

**Author Location** Nef (173–206)

**Epitope** MDDPEREVLEWRFSRLAFHHVARELHPEYFK-NC

**Neutralizing**

**Immunogen**

**Species (Isotype)** mouse

**References** Kaminchik *et al.* 1990

- NF1A1: Recognizes the Nef protein of the two isolates BH10 and LAV1 – low affinity. Kaminchik *et al.* [1990]

**No.** 1399

**MAb ID** polyclonal

**HXB2 Location** Nef (186–206)

**Author Location** Nef (185–205 LAI, BRU)

**Epitope** DSRLAFHHVARELHPEYFKNC

**Subtype** B

**Neutralizing**

**Immunogen** HIV-1 infection, vaccine

*Vector/Type:* protein, PLG microparticle  
*Strain:* B clade BRU, B clade LAI  
*HIV component:* Nef *Adjuvant:* Complete Freund's Adjuvant (CFA), PLG

**Species (Isotype)** mouse (IgG1)

**References** Moureau *et al.* 2002

- Nef encapsulated in poly(DL-lactide-co-glycolide) (PLG) had a more prolonged Ab response than Nef in PBS or in Freund's adjuvant (CFA), still strong after 7 months – the response was predominantly IgG1, a Th2 immune response – three linear epitopes, Nef 32-64, 118-167, and 185-205, were frequently recognized by the sera of mice immunized with Nef/PLG or Nef-CFA, but not after immunization with Nef in PBS, which



seemed to preferentially stimulate an Ab response to conformational epitopes. Moureau *et al.* [2002]

**No.** 1400  
**MAb ID** E7  
**HXB2 Location** Nef (192–206)  
**Author Location** Nef (192–206 IIIB)  
**Epitope** HHVARELHPEYFKNC  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** mouse (IgM)  
**References** Fujii *et al.* 1996d; Fujii *et al.* 1996b; Fujii *et al.* 1996a; Fujii *et al.* 1996c; Otake *et al.* 1994; Fujii *et al.* 1993

- E7: Insect cells expressing myristylated Nef proteins on their cell surface can induce cytolysis of unstimulated CD4+ cells – this response is not due to MHC restricted CTL activity – the cell surface of Nef expressing insect cells carry Nef that can be recognized by MAbs E7 and E9 but not F1. Fujii *et al.* [1996c]
- E7: Nef forms a homomeric oligomerizing structure, and using E7 and membrane immunofluorescence or immunoelectron microscopy, was shown to clusters on the surface of HIV-1 infected CD4+ cells. Fujii *et al.* [1996a]
- E7: A carboxy-terminal domain of Nef on the cell surface induces cytolysis of CD4+ T cells. Fujii *et al.* [1996b]
- E7: Soluble Nef inhibits proliferation of CD4+ cells, and Nef cross-linking by MAbs may induce anti-CD4 cytotoxic activity – sera from HIV+ individuals contain soluble Nef, thus this may be important for immune dysfunction and disease progression. Fujii *et al.* [1996d]
- E7: The C-term end of Nef is accessible to Abs at the cell surface – stained IIIB/M10, but not MN/M10, cells. Fujii *et al.* [1993]; Otake *et al.* [1994]

**No.** 1401  
**MAb ID** AE6  
**HXB2 Location** Nef (194–206)  
**Author Location** Nef (LAI)  
**Epitope** VARELHPEYFKNC  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type: protein HIV component: Nef*  
**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** C-term  
**Research Contact** Frank Jirik, Centre for Molecular Med and Therapeutics, U. B. C., Vancouver, B. C. Canada

- References** Chang *et al.* 1998
- AE6: The light and heavy chains of three MAbs (AG11, AE6, EH1) specific to C-terminus of NEF were cloned and variable regions sequenced – the complementarity determining regions (CDR) of AG11 and AE6 were highly related (95.1% at the DNA level) and bound LAI Nef, but not SF2 Nef – EH1 bound to SF2 and LAI and cross-competed AG11 and AE6 but had a distinctive CDR (57.9% similar to AG11) – single chain Abs were constructed from AG11 and EH1. Chang *et al.* [1998]

**No.** 1402

**MAb ID** AG11  
**HXB2 Location** Nef (194–206)  
**Author Location** Nef (LAI)  
**Epitope** VARELHPEYFKNC  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type: protein HIV component: Nef*  
**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** C-term  
**Research Contact** Frank Jirik, Centre for Molecular Med and Therapeutics, U. B. C., Vancouver, B. C. Canada

- References** Chang *et al.* 1998
- AG11: The light and heavy chains of three MAbs (AG11, AE6, EH1) specific to C-terminus of NEF were cloned and variable regions sequenced – the complementarity determining regions (CDR) of AG11 and AE6 were highly related (95.1% at the DNA level) and bound LAI Nef, but not SF2 Nef – EH1 bound to SF2 and LAI and cross-competed AG11 and AE6 but had a distinctive CDR (57.9% similar to AG11) – single chain Abs were constructed from AG11 and EH1 and subcloned into a eukaryotic expression vector with a green fluorescent protein marker to allow intracellular expression – the single chain Abs bind Nef intracellularly and may be useful to better understand the role of Nef and as a gene therapy model. Chang *et al.* [1998]

**No.** 1403  
**MAb ID** EH1  
**HXB2 Location** Nef (194–206)  
**Author Location** Nef (SF2)  
**Epitope** MARELHPEYKDC  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type: protein HIV component: Nef*  
**Species (Isotype)** mouse (IgG1κ)  
**Ab Type** C-term  
**Research Contact** Frank Jirik, Centre for Molecular Med and Therapeutics, U. B. C., Vancouver, B. C. Canada

- References** Chang *et al.* 1998
- EH1: The light and heavy chains of three MAbs (AG11, AE6, EH1) specific to C-terminus of NEF were cloned and variable regions sequenced – the complementarity determining regions (CDR) of AG11 and AE6 were highly related (95.1% at the DNA level) and bound LAI Nef, but not SF2 Nef – EH1 bound to SF2 and LAI and cross-competed AG11 and AE6 but had a distinctive CDR (57.9% similar to AG11) – single chain Abs were constructed from AG11 and EH1 and subcloned into a eukaryotic expression vector with a green fluorescent protein marker to allow intracellular expression – the single chain Abs bind Nef intracellularly and may be useful to better understand the role of Nef and as a gene therapy model. Chang *et al.* [1998]

**No.** 1404  
**MAb ID** 3B4B  
**HXB2 Location** Nef  
**Author Location** Nef

**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
*Adjuvant:* Incomplete Freund's Adjuvant (IFA)  
**Species (Isotype)** transgenic mouse (IgM)  
**References** Kawai *et al.* 2003  
**Keywords** antibody generation, complement

- 3B4B: The goal of this study was to elicit anti-Nef IgM human Abs in trans-chromosome mice that carry human chromosomes responsible for Ig production. These mice were immunized with recombinant Nef protein. Two human heavy chain, mouse light chain anti-Nef IgM were obtained, 3B4B and 3H3E; 3B4B was able to stain MOLT4/IIIB cells with greater intensity. The hope was that these human IgM anti-Nef chimeric Abs would activate complement mediated cytotoxicity; C3 deposition was induced but not at high enough levels to induce lysis. Kawai *et al.* [2003] (**antibody generation, complement**)

**No.** 1405  
**MAb ID** 3H3E  
**HXB2 Location** Nef  
**Author Location** Nef  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *HIV component:* Nef  
*Adjuvant:* Complete Freund's Adjuvant (CFA)  
**Species (Isotype)** transgenic mouse (IgM)  
**References** Kawai *et al.* 2003  
**Keywords** antibody generation, complement

- 3H3E: The goal of this study was to elicit anti-Nef IgM human Abs in trans-chromosome mice that carry human chromosomes responsible for Ig production. These mice were immunized with recombinant Nef protein. Two human heavy chain, mouse light chain anti-Nef IgM were obtained, 3B4B and 3H3E; 3B4B was able to stain MOLT4/IIIB cells with greater intensity. The hope was that these human IgM anti-Nef chimeric Abs would activate complement mediated cytotoxicity; C3 deposition was induced but not at high enough levels to induce lysis. Kawai *et al.* [2003] (**antibody generation, complement**)

**No.** 1406  
**MAb ID** 6.1  
**HXB2 Location** Nef  
**Author Location** Nef (JRCSF)  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** mouse  
**References** Ranki *et al.* 1995

- 6.1: Raised against CNS primary isolates, stains astrocytes more densely than other Nef MAbs – Nef expression associated with dementia. Ranki *et al.* [1995]
- 6.1: NIAID Repository number 1123. Ranki *et al.* [1995]

**No.** 1407  
**MAb ID** NF2B2  
**HXB2 Location** Nef  
**Author Location** Nef (20–78 BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* Nef  
**Species (Isotype)** mouse  
**References** Kaminchik *et al.* 1990

- NF2B2: NIH AIDS Research and Reference Reagent Program: 456.
- NF2B2: Recognizes the Nef protein of the two isolates BH10 and LAV1. Kaminchik *et al.* [1990]

**No.** 1408  
**MAb ID** NF3A3  
**HXB2 Location** Nef  
**Author Location** Nef (20–78 BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* Nef  
**Species (Isotype)** mouse  
**References** Kaminchik *et al.* 1990

- NF3A3: Recognizes the Nef protein of the two isolates BH10 and LAV1 – low affinity. Kaminchik *et al.* [1990]

**No.** 1409  
**MAb ID** NF8B4  
**HXB2 Location** Nef  
**Author Location** Nef (BH10)  
**Epitope**  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade BH10  
*HIV component:* Nef  
**Species (Isotype)** mouse  
**References** Kaminchik *et al.* 1990

- NF8B4: Does not recognize Nef CNBr cleavage products – recognizes intact BH10 Nef but not LAV1 Nef. Kaminchik *et al.* [1990]

**No.** 1410  
**MAb ID** polyclonal  
**HXB2 Location** Nef  
**Author Location** Nef  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade LAI, SIV *HIV component:* gp120, Nef, Tat  
*Adjuvant:* AS02A (oil-in-water emulsion, 3D-monophosphoryl lipid A, QS21), AS06 (CpG, aluminum hydroxide)  
**Species (Isotype)** macaque (IgG)  
**References** Voss *et al.* 2003

**Keywords** adjuvant comparison, variant cross-recognition or cross-neutralization

- Monkeys were immunized with different combinations of gp120/NefTat/SIV-Tat three times over a three-month time period and intravenously challenged with SHIV 89.6P four weeks after the last immunization. Vaccination induced anti-Tat, -Nef and -gp120 Ab responses that decreased until challenge. Neutralizing Ab responses against HIV-1 MN and HIV-1 W61D were observed. Vaccination with the combination of all three proteins reduced viral load and kept animals from a CD4+ T cell decline, preventing AIDS for more than 2.5 years. The adjuvant AS02A elicited NABs and protected from disease, while AS06 did not. gp120 alone or TatNef/SIV-Tat without gp120 could not protect from disease. Voss *et al.* [2003] (**adjuvant comparison, variant cross-recognition or cross-neutralization**)

**No.** 1411

**MAb ID** AE6

**HXB2 Location** Nef

**Author Location** Nef

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** mouse

**Ab Type** C-term

**Research Contact** James Hoxie, Div of AIDS, NIAID, NIH

**References** Tornatore *et al.* 1994; Greenway *et al.* 1994

- AE6: NIH AIDS Research and Reference Reagent Program: 709.

#### IV-C-19 HIV-1 Antibodies

**No.** 1412

**MAb ID**

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)**

**References** Goepfert 2003

**Keywords** review

- A general review of anti-HIV human immune responses and the implications of these responses for vaccines, summarizing neutralizing antibodies, CD4+ and CD8+ T cell responses. A general overview of methods used to study these responses is presented. Goepfert [2003] (**review**)

**No.** 1413

**MAb ID**

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Adjuvant:* CD40, CD80, CD86, Complete Freund's Adjuvant (CFA), GM-CSF, IFN $\gamma$ , IL-12, IL-15, IL-18, IL-1 $\alpha$ , IL-2, IL-2/Ig, IL-4, IL-7, CpG immunostimulatory sequence (ISS), Tumor Necrosis Factor  $\alpha$  (TNF $\alpha$ ), Tumor Necrosis Factor  $\beta$  (TNF $\beta$ ), M-CSF, IL-8, RANTES

**Species (Isotype)**

**References** Mitchison & Sattentau 2005

**Keywords** adjuvant comparison, review, Th1, Th2

- Review summarizes mechanisms of immunoregulation relevant for new vaccine development, with a brief summary of adjuvant triggering innate immunity through Toll-like receptors (TLRs), Nod molecules, and other activators. DNA encoded adjuvants that have been tested in DNA vaccines are summarized. The balance between Th1 (CTL activating) and Th2 (B cell activating) responses is discussed, and it is noted that BALB/c mice are predominately Th2 responders, C57BL Th1. Mitchison & Sattentau [2005] (**adjuvant comparison, Th1, Th2, review**)

**No.** 1414

**MAb ID**

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen**

**Species (Isotype)** human

**References** Piontkivska & Hughes 2006

**Keywords** escape

- The greatest amino acid diversity is found in sites in the HIV genome that are spanned by antibody epitopes. Sites spanned by CTL epitopes, not but not by antibody epitopes, showed reduced amino acid diversity even in comparison to non-epitope sites. However, mutations within CTL epitopes were more likely to be convergent than mutations within antibody epitopes. These patterns were consistent both in Gag and Env. Piontkivska & Hughes [2006] (**escape**)

**No.** 1415

**MAb ID** 13b18

**HXB2 Location** HIV-1

**Author Location** (LAI)

**Epitope**

**Subtype** B

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgG)

**Ab Type** gp120 CD4BS

**References** Koefoed *et al.* 2005

**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13b18: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected

library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, including this one, as they could be blocked with sCD4 and murine anti-CD4BS Abs. Fab 13b18 was not neutralizing. Koefoed *et al.* [2005] (**antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain**)

**No.** 1416  
**MAb ID** 13b23  
**HXB2 Location** HIV-1  
**Author Location** (LAI)  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**Ab Type** gp120 C1  
**References** Koefoed *et al.* 2005  
**Keywords** antibody binding site definition and exposure, antibody generation, antibody sequence variable domain, kinetics

- 13b120: IgG antibody phage display libraries were created from HIV-1 + individuals using unselected PBMC or after pre-selection of PBMC with gp120 using affinity columns. This was one of 2 gp120 Abs from the unselected library; 9 Abs were obtained from a 10-fold smaller pre-selected library. This approach offers an alternative to generating libraries from bone marrow, which is often difficult to obtain. Most of the Fabs bound to the CD4BS, but not 13b120; this Fab was partially inhibited by anti-C1 mAb MAG45, and enhanced by CD4i MAb b17 and anti-C1 MAb 1331290. Koefoed *et al.* [2005] (**antibody binding site definition and exposure, antibody generation, kinetics, antibody sequence variable domain**)

**No.** 1417  
**MAb ID** LA28  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human  
**Ab Type** gp120 CCR5BS  
**References** Haynes *et al.* 2005  
**Keywords** antibody binding site definition and exposure

- LA28: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. LA28 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

**No.** 1418  
**MAb ID** LF17  
**HXB2 Location** HIV-1  
**Author Location**

**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)** human  
**Ab Type** gp120 CCR5BS  
**References** Haynes *et al.* 2005  
**Keywords** antibody binding site definition and exposure

- LF17: Of 35 Env-specific MAbs tested, only 2F5, 4E10, IgG1b12, and two CD4BS adjacent MAbs (A32 and 1.4G) and gp41 MAbs (2.2B and KU32) had binding patterns suggesting polyspecific autoreactivity, and similar reactivities may be difficult to induce with vaccines because of elimination of such autoreactivity. LF17 has no indication of polyspecific autoreactivity. Haynes *et al.* [2005] (**antibody binding site definition and exposure**)

**No.** 1419  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Fournier *et al.* 2002b

- Purified B lymphocytes secrete only a fraction of Ig and anti-HIV-1 Ab compared with unfractionated cells because monocytes and natural killer cells enhance both secretions by cell-to-cell contacts, involving adhesion and CD27, CD80 costimulatory molecules and IL-6 – cell-to-cell contacts and soluble factors induce maturation of activated B cells *in vitro* to allow prolonged survival and terminal differentiation. Fournier *et al.* [2002b]

**No.** 1420  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Fournier *et al.* 2002a

- An early and sustained fall in plasma viral load to below detection was observed in 17 HAART responders while HIV-1 RNA remained detectable in 13 incomplete responders – HIV-1 specific Ab secretion decreased in parallel with plasma viral load – HIV-1 specific Abs became negative in only six responders, and was correlated with greater increases of CD4 T-cell counts and higher levels of HIV-specific IgA secretion at baseline – persistent immune activation may be due to residual HIV antigen. Fournier *et al.* [2002a]

**No.** 1421  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Subbramanian *et al.* 2002

- Sera from 39 patients were used to study the relative prevalence of neutralizing Abs (NAbs), ADCC-Abs and enhancing Abs – 69% of the sera were positive for NAbs but only 39% could neutralize in the presence of complement – 60% had ADCC Abs – 72% mediated the enhancement of infection in the presence of complement. Subbramanian *et al.* [2002]

**No.** 1422

**MAb ID** polyclonal

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgA, IgG1)

**References** Battle-Miller *et al.* 2002

- In a study of HIV-1 infected women, ADCC Abs were detected in 16% (12/51) of cervicovaginal fluids, and 56% (25/45) of serum samples – 3 women had ADCC in cervical lavage fluids, but not sera, suggesting local production. Battle-Miller *et al.* [2002]

**No.** 1423

**MAb ID** polyclonal

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgA1, IgA2, IgM)

**References** Wu & Jackson 2002

- IgA1 accounted for the majority of anti-HIV-1 IgA in the saliva in HIV-1 infected individuals – there was no anti-gp41 IgA in saliva, in contrast to plasma – lower levels of IgA and IgM were found in saliva than in plasma. Wu & Jackson [2002]

**No.** 1424

**MAb ID** polyclonal

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgA, IgG)

**References** Oelemann *et al.* 2002

- A urine based commercial EIA kit from Calypte Biomedical Corporation, Berkeley, CA was found to work well as a primary screening for HIV in Brazilian samples – 76 HIV+ samples were correctly identified (100% sensitivity), and 278/284 negative samples 97.9% specificity. Oelemann *et al.* [2002]

**No.** 1425

**MAb ID** polyclonal

**HXB2 Location** HIV-1

**Author Location** HIV-1

**Epitope**

**Neutralizing** no

**Immunogen** HIV-1 infection

**Species (Isotype)** human (IgE)

**References** Pellegrino *et al.* 2002; Secord *et al.* 1996

- Pediatric long term survivors (LTS) have been found to carry HIV-1 specific IgE – serum from these children inhibit HIV-1 production in culture, but this inhibition did not seem to be due to neutralization, rather due to a cytotoxic event – serum lost the HIV-1 inhibitory effect when depleted of IgE. Pellegrino *et al.* [2002]
- HIV-specific IgE found in clinically healthy HIV-1 infected children. Secord *et al.* [1996]

**No.** 1426

**MAb ID** polyclonal

**HXB2 Location** HIV-1

**Author Location** gp120 and p55

**Epitope**

**Neutralizing** no

**Immunogen** vaccine

*Vector/Type:* vaccinia *Strain:* B clade 89.6

*HIV component:* Env, Gag-Pol *Adjuvant:*

*E. coli mutant heat labile enterotoxin (LT-R72)*

**Species (Isotype)** macaque

**References** Ambrose *et al.* 2003

**Keywords** genital and mucosal immunity

- Systemic priming with rVVs expressing HIV-1 Env and SHIV Gag-Pol followed by intragastric and intranasal mucosal boosting of LT(R192G) and aldrithiol-2 (AT-2)-inactivated SHIV induced SHIV-specific IgA and IgG plasma and mucosal Abs. Viral loads in vaccinated animals were reduced after vaginal challenge with SHIV 89.6. Ambrose *et al.* [2003] (**genital and mucosal immunity**)

**No.** 1427

**MAb ID** polyclonal

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Subtype** B

**Neutralizing** P

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Binley *et al.* 2004

**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

- 93 viruses from different clades were tested for their neutralization cross-reactivity using a panel of HIV monoclonal antibodies, and a plasma from an HIV-1 + donor infected with a B clade virus. The plasma antibodies broadly neutralized viruses from many clades, with a slight preference for B clade. Binley *et al.* [2004] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 1428

**MAb ID** polyclonal

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Subtype** A, B

**Neutralizing L**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**Ab Type** gp120 V3  
**References** Krachmarov *et al.* 2005  
**Keywords** antibody binding site definition and exposure, subtype comparisons, variant cross-recognition or cross-neutralization

- Sera from 23 subtype A infected individuals from Cameroon have antibodies that react strongly with subtype A and subtype B V3 loops in fusion proteins, and neutralize SF162 pseudotypes, while sera from 47 subtype B infected individuals reacted only with subtype B. The sera from Cameroon do not neutralize primary A or B isolates, due to indirect masking by the V1/V2 domain rather than due to loss of the target epitope. Krachmarov *et al.* [2005] (**antibody binding site definition and exposure, variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 1429  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location** (HXB2)  
**Epitope**  
**Subtype** B  
**Neutralizing** yes  
**Immunogen** vaccine  
*Vector/Type:* vesicular stomatitis virus (VSV) with protein boost *Strain:* B clade HXB2 *HIV component:* gp41 MPER  
*Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** rabbit  
**References** Luo *et al.* 2006  
**Keywords** vaccine antigen design

- gp41 and p15E of the porcine endogenous retrovirus (PERV) share structural and functional similarities, and epitopes in the membrane proximal region of p15E are able to elicit NAbs upon immunization with soluble p15E. Rabbits immunized with a VSV recombinant expressing an HIV-1 membrane-proximal external region (MPER) fused to PERV p15E, with a fusion p15E-HIV MPER protein boost, elicited HIV specific NAbs in 3/9 rabbits each for two different constructs, with and without the E2 region of p15E. Luo *et al.* [2006] (**vaccine antigen design**)

**No.** 1430  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** multiple  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)  
**References** Parekh & McDougal 2005  
**Keywords** acute/early infection, assay development, assay standardization/improvement

- This paper describes IgG-Capture BED-EIA, which detects the increasing proportion of HIV-1-IgG relative to total IgG and can be used to detect early infection and incidence data in cross-sectional and sentinel surveillance studies, and is robust for use with multiple HIV-1 subtypes. Parekh & McDougal [2005] (**assay development, acute/early infection, assay standardization/improvement**)

**No.** 1431  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* fixed fusion-intermediate  
*Strain:* B clade US005.11, FASH isolate  
*HIV component:* Env

**Species (Isotype)** mouse  
**References** Zipeto *et al.* 2005  
**Keywords** co-receptor, vaccine antigen design

- HIV-1 fusion complexes were prepared from cell lines expressing R5 HIV-1 gp120/gp41 and CD4-CCR5. Fusion complexes were prepared at different temperatures (21, 30 or 37 degrees C) with different fixative combinations, and used to immunize mice. Complexes prepared at 37 degrees were the most immunogenic, suggesting that fixation of multiple conformation intermediates may be helpful. Neutralizing Abs were raised against both R5 (strain BaL) and X4 (strain 213) viruses. Zipeto *et al.* [2005] (**co-receptor, vaccine antigen design**)

**No.** 1432  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** B  
**Neutralizing** no  
**Immunogen** vaccine  
*Vector/Type:* protein *Strain:* B clade ADA  
*HIV component:* Env fragments in a pre-fusion state trimer  
*Adjuvant:* Complete Freund's Adjuvant (CFA), Incomplete Freund's Adjuvant (IFA)

**Species (Isotype)** rabbit  
**References** Qiao *et al.* 2005  
**Keywords** antibody binding site definition and exposure, vaccine antigen design, vaccine-specific epitope characteristics

- A gp140 prefusion state trimer composed of gp41 truncated at Lys665, and gp120 C1 and C5 (topless gp140), was engineered and used to immune rabbits. No NAbs were raised, although the polyclonal sera recognized many regions of the truncated Env. Qiao *et al.* [2005] (**antibody binding site definition and exposure, vaccine antigen design, vaccine-specific epitope characteristics**)

**No.** 1433

**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** vaccine  
*Vector/Type:* DNA prime with modified vaccinia Ankara (MVA) boost *HIV component:* Env, Gag-Pol  
**Species (Isotype)** macaque  
**References** Sadagopal *et al.* 2005  
**Keywords** vaccine-induced epitopes

- 22/23 macaques vaccinated with a DNA Gag-Pol\_Env prime and vaccinia virus Ankara boost controlled SHIV viremia until euthanasia at 200 weeks post-challenge. All animals had low or undetectable viral loads, normal CD4 counts, and high titers of neutralizing antibodies. Most animals recognized 2 CD8 epitopes and 1 CD4 epitope, with up to 3 CD8 and 5 CD4 epitopes. Most T-cell epitopes were in Gag, though some were in Env. Sadagopal *et al.* [2005] (**vaccine-induced epitopes**)

**No.** 1434  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**  
**References** Haynes & Montefiori 2006  
**Keywords** antibody binding site definition and exposure, co-receptor, escape, genital and mucosal immunity, neutralization, optimal epitope, review, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- This review describes the effectiveness of the current HIV-1 immunogens in eliciting neutralizing antibody responses to different clades of HIV-1. It also summarizes different evasion and antibody escape mechanisms, as well as the most potent neutralizing MAbs and their properties. MAbs reviewed in this article are: 2G12, IgG1b12, 2F5, 4E10, A32, 447-52D and, briefly, D50. Novel immunogen design strategies are also discussed. Haynes & Montefiori [2006] (**antibody binding site definition and exposure, co-receptor, genital and mucosal immunity, neutralization, optimal epitope, vaccine antigen design, variant cross-recognition or cross-neutralization, escape, review, subtype comparisons**)

**No.** 1435  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** B  
**Neutralizing**  
**Immunogen** HIV-1 infection, in vitro stimulation or selection  
**Species (Isotype)** human (IgA, IgG)

**References** Holl *et al.* 2006b

**Keywords** dendritic cells, kinetics, neutralization

- Inhibition of R5 HIV replication by monoclonal and polyclonal IgGs and IgAs in immature monocyte-derived dendritic cells (iMDDCs) was evaluated. It was shown that anti-HIV IgG was able to inhibit HIV-1 replication more efficiently in iMDDCs than in PBLs, while no such activity was observed for polyclonal IgA. The kinetics of IgG addition suggested that the inhibition occurred early in HIV infection. No induction of maturation was observed. Two mechanisms of HIV inhibition in iMDDCs by IgG are described: i) neutralization of HIV infectivity by Fab parts of IgG, and ii) inhibition of HIV infection via FcγRII or FcγRI expressed on target cells. Holl *et al.* [2006b] (**neutralization, kinetics, dendritic cells**)

**No.** 1436  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Subtype** C  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human  
**References** Lakhashe *et al.* 2007  
**Keywords** subtype comparisons, variant cross-recognition or cross-neutralization

- Plasma samples collected from HIV-1 infected individuals in India showed extensive cross-neutralizing response against a panel of primary subtype C isolates, suggesting presence of shared neutralization determinants among subtype C in India. Sequence analysis showed limited genetic diversity of Indian subtype C compared to subtype C from Africa. Lakhashe *et al.* [2007] (**variant cross-recognition or cross-neutralization, subtype comparisons**)

**No.** 1437  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing** L, P  
**Immunogen** HIV-1 infection, HIV-2 infection  
**Species (Isotype)** human  
**References** Rodriguez *et al.* 2007  
**Keywords** HIV-2, neutralization, variant cross-recognition or cross-neutralization

- Neutralizing Ab responses against 7 heterologous primary isolates and 1 laboratory strain were compared in HIV-1 and HIV-2 infections. HIV-2 infection was found to be characterized by a broad, low magnitude neutralization response, while HIV-1 infection was characterized by a more narrow, higher magnitude response. A significant positive association between the magnitude of neutralization response and viremia was observed for both HIV-1 and HIV-2. Cross-neutralization of HIV-2 by HIV-1 plasma and vice versa was very rare. Rodriguez *et al.* [2007] (**HIV-2, neutralization, variant cross-recognition or cross-neutralization**)

**No.** 1438

**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen**  
**Species (Isotype)**

**References** Humbert & Dietrich 2006

**Keywords** antibody binding site definition and exposure, assay standardization/improvement, escape, immune evasion, neutralization, vaccine antigen design

- This review discusses different mechanisms of Ab mediated neutralization and different mechanisms of NAb viral escape and immune evasion. Furthermore, recent research on the protective role of NAb in HIV-1 infection, as well as preliminary vaccines and immunogens are summarized. Detection of NAb by neutralization assays and the importance and requirements of assay standardization are highlighted. Humbert & Dietrich [2006] (**antibody binding site definition and exposure, immune evasion, neutralization, vaccine antigen design, escape, assay standardization/improvement**)

**No.** 1439

**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human

**References** Killian *et al.* 2006

**Keywords** acute/early infection, dynamics, early treatment, HAART, ART

- The influence of ART on the HIV-specific antibody titers during primary HIV-1 infection was examined in treated and untreated individuals as well as individuals that discontinued ART. It was found that the Ab levels gradually increased in untreated patients, and continued to increase after the viral load set point, until approximately 40 weeks postinfection when an Ab plateau was reached. Early ART-treated patients had low Ab titers associated with an early and substantial reduction in virus replication. Patients that discontinued early ART experienced a rebound of virus replication associated with a rapid rise in Ab titer. The results indicate that early ART influences typical evolution of HIV-1 specific Ab response. Killian *et al.* [2006] (**acute/early infection, dynamics, early treatment, HAART, ART**)

**No.** 1440

**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG, IgG1, IgG3, IgG2, IgG4)

**References** Adalid-Peralta *et al.* 2006

**Keywords** acute/early infection, dynamics, early treatment, HAART, ART

- This study examined the impact of early HAART on antibody quality and production in patients with primary HIV-1 infection by comparing treated and untreated patients. Responses against pol, env and gag were analysed. HAART affected the concentration of all anti-HIV IgG subclasses studied, as treated patients showed lower Ab responses. However, HAART did not change the ratio between the Ab subclasses. Furthermore, the avidity of anti-HIV-1 IgG did not differ between the two patient groups, indicating that the effect of HAART is only quantitative and limited to the final stages of the anti-HIV B-cell response. Adalid-Peralta *et al.* [2006] (**acute/early infection, dynamics, early treatment, HAART, ART**)

**No.** 1441

**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing** L, P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human

**References** Deeks *et al.* 2006

**Keywords** acute/early infection, autologous responses, neutralization, variant cross-recognition or cross-neutralization

- Neutralizing Ab responses were measured against autologous and heterologous isolates in acutely and chronically HIV-1 infected patients. Individuals with acute infection showed lower neutralizing Ab response against both autologous and heterologous viruses than the chronically infected patients, and had a higher neutralizing titers directed against earlier viruses than against contemporaneous viruses. In chronically infected patients, the level of neutralizing Abs against heterologous viruses was positively correlated with the level of viremia, indicating that HIV replication continuously drives the production of Abs that cross-neutralize primary isolates. Furthermore, the correlation of neutralizing Abs against autologous viruses and viremia was negative, indicating that these Abs may contribute to the control of HIV-1 replication. In addition, neutralizing Ab response against contemporaneous viruses in chronic infection could be detected, although it was low. These results suggest that there might exist limits to the capacity of HIV-1 to evolve continuously in response to neutralizing Abs. Deeks *et al.* [2006] (**autologous responses, neutralization, variant cross-recognition or cross-neutralization, acute/early infection**)

**No.** 1442

**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing** P  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human

**References** Barin *et al.* 2006

**Keywords** mother-to-infant transmission, neutralization, variant cross-recognition or cross-neutralization



- The association between mother-to-child-transmission (MTCT) and maternal neutralizing Abs to heterologous primary isolates of HIV-1 clades B, F, CRF01\_AE and CRF02\_AG was examined. An association between higher titer of maternal neutralizing Abs to heterologous HIV-1 strain of the same clade (CRF01\_AE) and lower rate of MTCT was observed, but only for the intrapartum transmission. No association was found for in utero transmission or for any of the other clades tested. These results indicate that neutralizing Abs might have a role in the natural prevention of late perinatal HIV transmission. Barin *et al.* [2006] (**neutralization, variant cross-recognition or cross-neutralization, mother-to-infant transmission**)

No. 1443  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human

**References** Dickover *et al.* 2006

**Keywords** autologous responses, escape, mother-to-infant transmission, neutralization

- The role of maternal autologous NABs in selective transmission of HIV-1 escape variants to their infants was examined. In utero transmitting mothers were significantly less likely to have autologous NABs at delivery than nontransmitting mothers, while no difference between intrapartum transmitters and nontransmitters was observed. In addition, the infecting HIV-1 strains found in the infants were more closely related to maternal autologous NAB escape variants, suggesting that neutralizing Abs may have both protective and selective effects. However, sequence analyses of these HIV-1 strains, transmitted in the presence of maternal NABs, showed that they had features of both sensitive and escape maternal HIV-1 strains. It is suggested that NAB sensitive strains were transmitted from the mothers to their children, and that these strains rapidly evolved to acquire escape mutations due to the presence of maternal NABs in the infants. These results suggest that neutralizing Abs can promote rapid evolution of HIV-1 in infected children. Dickover *et al.* [2006] (**autologous responses, neutralization, escape, mother-to-infant transmission**)

No. 1444  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human

**References** Bailey *et al.* 2006a

**Keywords** autologous responses, HAART, ART, neutralization

- The amount of env gene diversity, the lengths of variable loops, and the number of N-linked glycosylation sites were observed lower in elite suppressors (ES) than in patients on HAART and in untreated chronically infected individuals. Also, the titers of NABs against two HIV-1 lab strains was shown to be lower in ES and HAART-treated patients than in untreated viremic individuals. However, despite these differences, the titers of NAB against autologous virus did not differ significantly between the three groups of patients. In addition, there was no difference in the titer of NABs against plasma viruses and against proviral variants in the ES. These results suggest that NAB do not play a dominant role in the maintenance of viral suppression in elite suppressors. Bailey *et al.* [2006a] (**autologous responses, neutralization, HAART, ART**)

No. 1445  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgG)

**References** Le Guillou-Guillemette *et al.* 2006

**Keywords** binding affinity, HAART, ART, memory cells

- The avidity of anti-HIV-1 IgG during HAART was observed to progressively decrease in patients, however, the B-cell subset depleted at the chronic stage of infection was shown to increase during the treatment. The increase concerned the naive B-cells secreting new antibodies with low affinity as the HIV antigen levels are lower under HAART. Investigation of the cellular, humoral and innate immune responses showed that HAART induced different immune restoration patterns in patients. It is suggested that the IgG avidity index is a weak marker of the restoration of humoral immune function in HIV-1 infected patients under HAART. Le Guillou-Guillemette *et al.* [2006] (**memory cells, binding affinity, HAART, ART**)

No. 1446  
**MAb ID** polyclonal  
**HXB2 Location** HIV-1  
**Author Location**  
**Epitope**  
**Neutralizing**  
**Immunogen** HIV-1 infection  
**Species (Isotype)** human (IgA, IgE, IgG, IgM)

**References** Hasson *et al.* 2006

**Keywords** HAART, ART, rate of progression, Th2

- Treatment of HIV-1 infected patients with the entry inhibitor ENF induced no change in patient's total IgM, IgG and IgA, however, a significant increase of IgE was observed in all the patients. A high proportion of the patients with elevated levels of IgE were characterized by advanced disease. However, the positive outcome of ENF treatment increasing the level of CD4 was observed in the patients irrespectively of their IgE levels. Hasson *et al.* [2006] (**HAART, ART, Th2, rate of progression**)

No. 1447

**MAb ID** polyclonal

**HXB2 Location** HIV-1

**Author Location**

**Epitope**

**Neutralizing**

**Immunogen** HIV-1 infection

**Species (Isotype)** human

**References** Titanji *et al.* 2006

**Keywords** acute/early infection, HAART, ART, memory cells

- The percentage of memory B-cells was shown to progressively decrease during the course of HIV-1 infection, and was correlated to the CD4+ T-cell counts, thus suggested to represent a marker of disease progression. In addition, patients with primary and chronic HIV-1 infection showed a decrease in the Ab titers to other viral and bacterial pathogens, indicating early occurrence of a defect in the B-cell compartment leading to a decline of serologic memory and immune response. However, this was not observed for LTNPs. Antiretroviral therapy did not restore serologic memory irrespectively of when the treatment was initiated. Titanji *et al.* [2006] (**memory cells, acute/early infection, HAART, ART**)

No. 1448

**MAb ID** polyclonal

**HXB2 Location** HIV-1

**Author Location** HIV-1

**Epitope**

**Neutralizing**

**Immunogen** vaccine

*Vector/Type:* adenovirus type 5 (Ad5)

*Strain:* B clade HXB2, B clade NL43,

B clade BaL, A clade 92RW020, C clade

97ZA012 *HIV component:* Env, Gag-Pol

**Species (Isotype)** human

**References** Catanzaro *et al.* 2006

**Keywords** neutralization, subtype comparisons, vaccine antigen design, variant cross-recognition or cross-neutralization

- 18 of 30 patients immunized with rAd5 vector HIV-1 clade B gag-pol and clade A, B and C Env vaccine had vaccine-induced Ab response detected by ELISA, which also was shown to be dose-dependent. 28 of 30 patients were positive for an EnvB-specific Ab response by Western-blot 4 weeks after immunization. A greater magnitude of response was detected to EnvC and EnvA than to EnvB. Weak responses to Gag were detected. No neutralizing Abs were detected. Catanzaro *et al.* [2006] (**neutralization, vaccine antigen design, variant cross-recognition or cross-neutralization, subtype comparisons**)

## IV-D

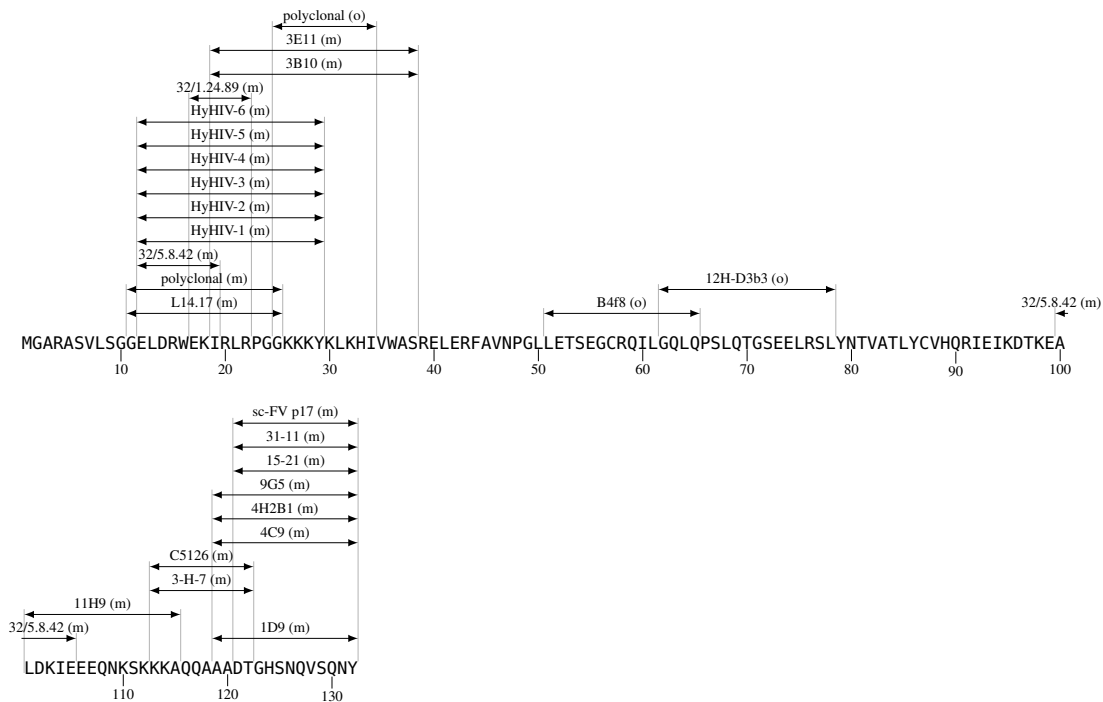
# Maps of MAb Locations Plotted by Protein

Linear epitopes less than of 21 amino acids or less are shown with their antibody ID and the experimental species.

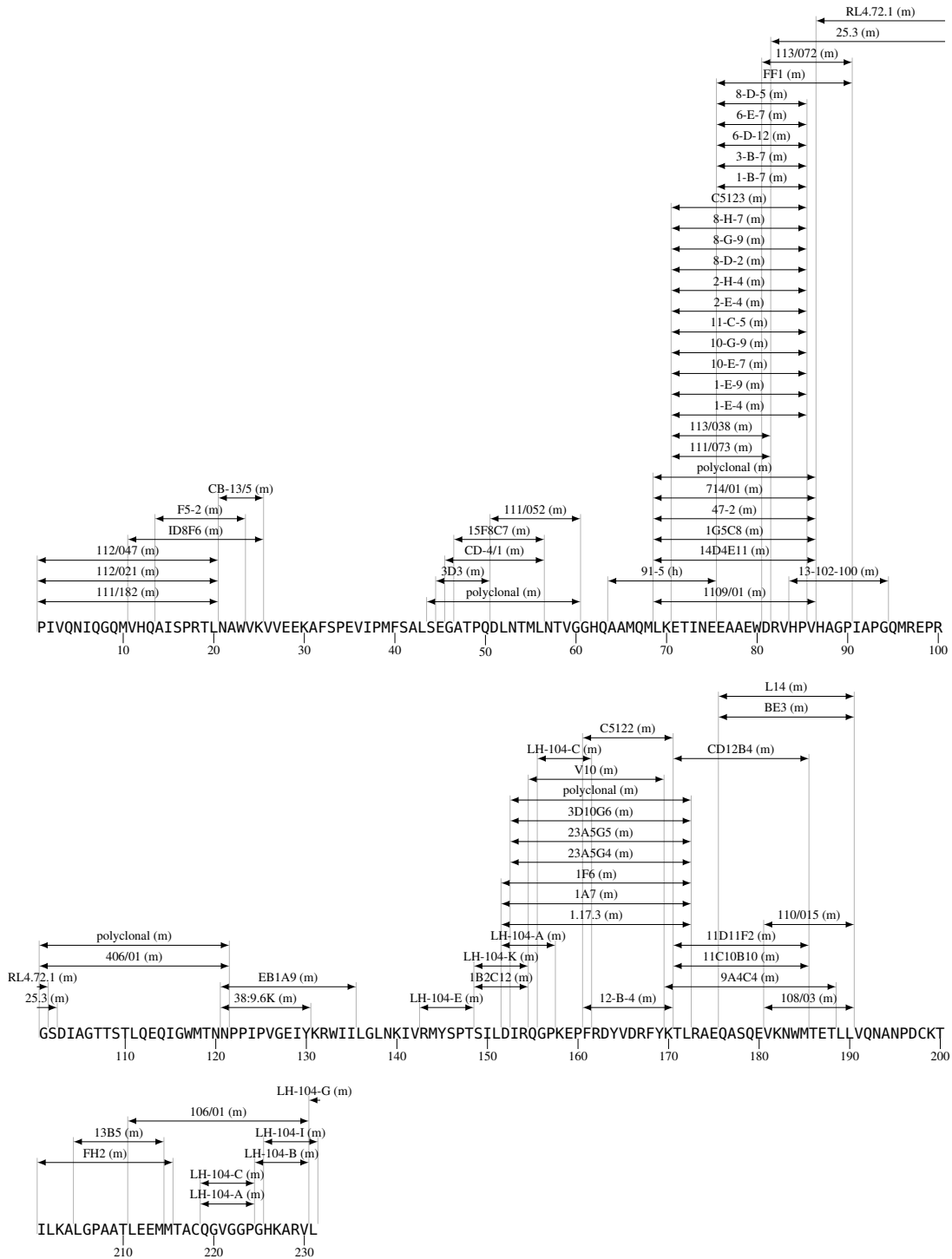
Key	Species
h	human
p	non-human primate
m	murine
o	other

**Table IV-D.1:** The species that the epitope was generated in and derived from.

### IV-D-1 p17 Ab Epitope Map

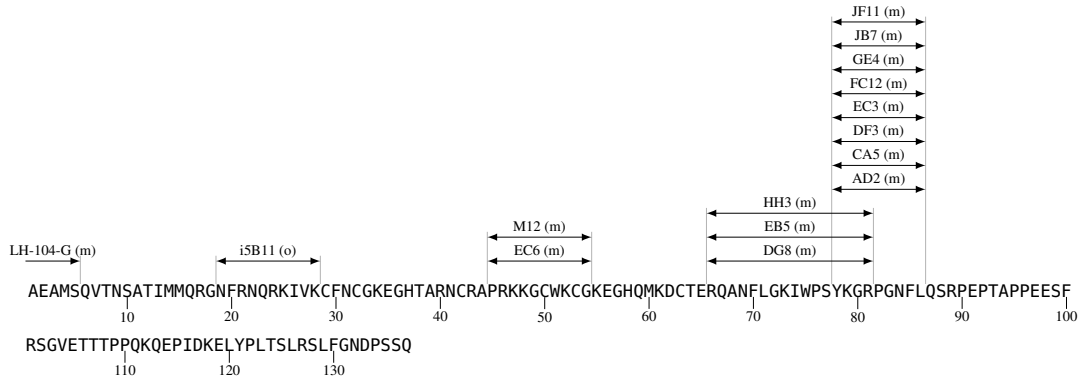


IV-D-2 p24 Ab Epitope Map



B Cell

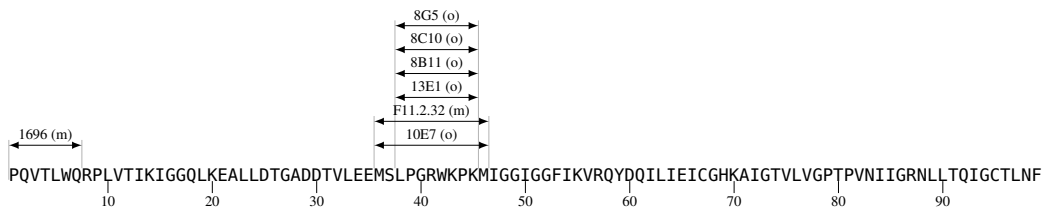
IV-D-3 p2p7p1p6 Ab Epitope Map



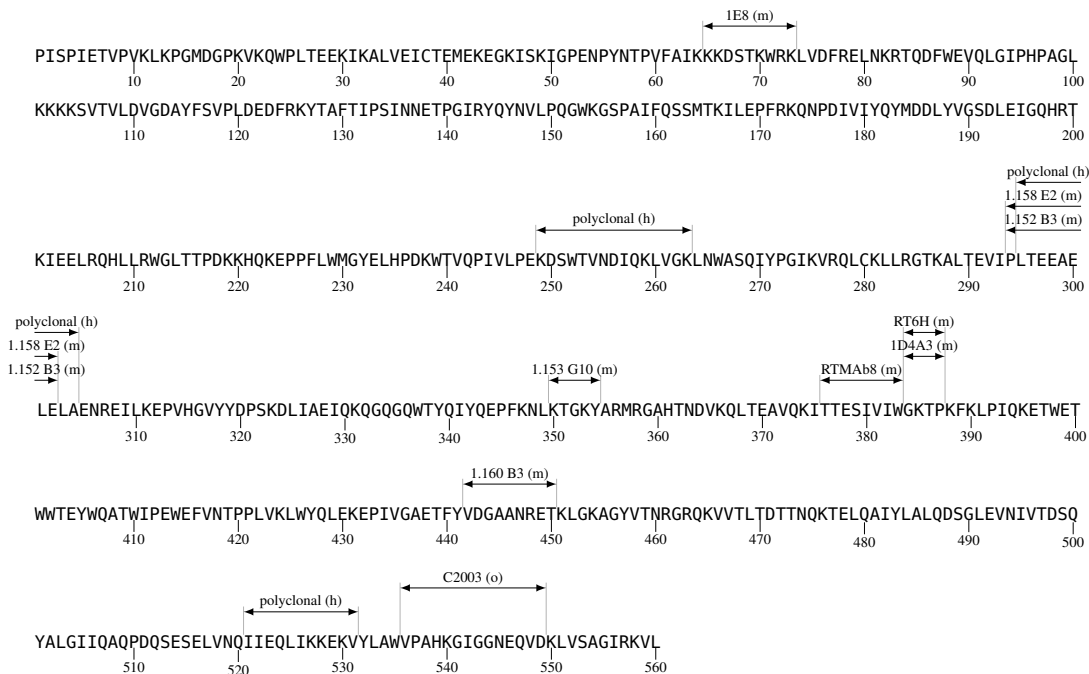
IV-D-4 Gag/Pol TF Ab Epitope Map



IV-D-5 Protease Ab Epitope Map

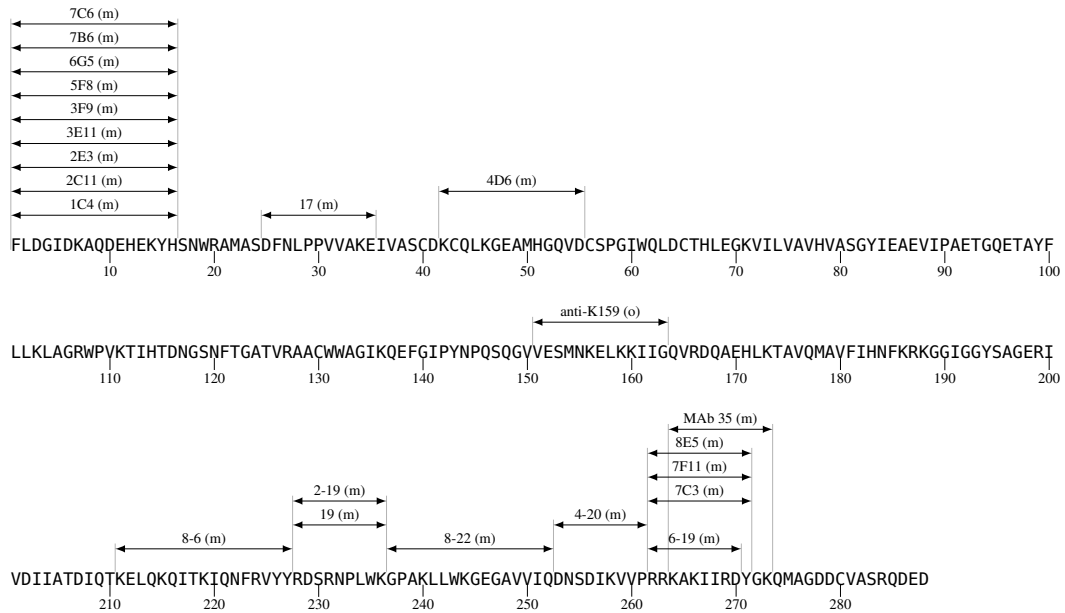


IV-D-6 RT Ab Epitope Map

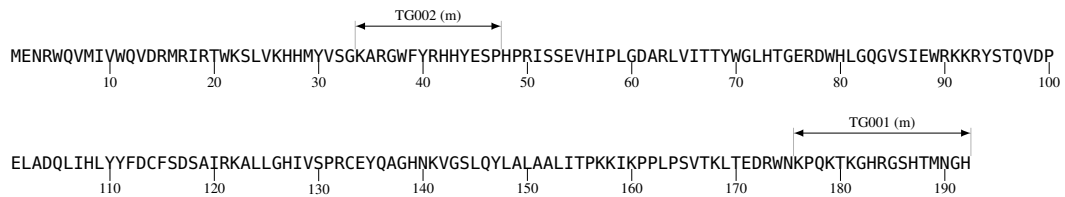


B Cell

IV-D-7 Integrase Ab Epitope Map



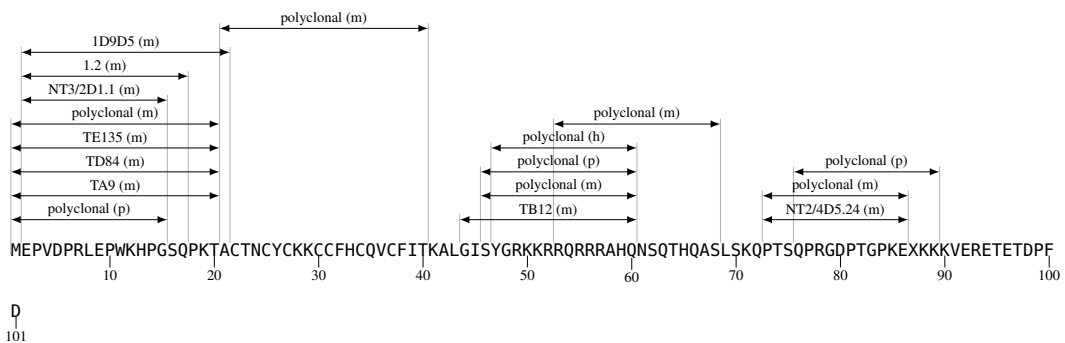
IV-D-8 Vif Ab Epitope Map



IV-D-9 Vpr Ab Epitope Map



IV-D-10 Tat Ab Epitope Map



D  
101

B Cell

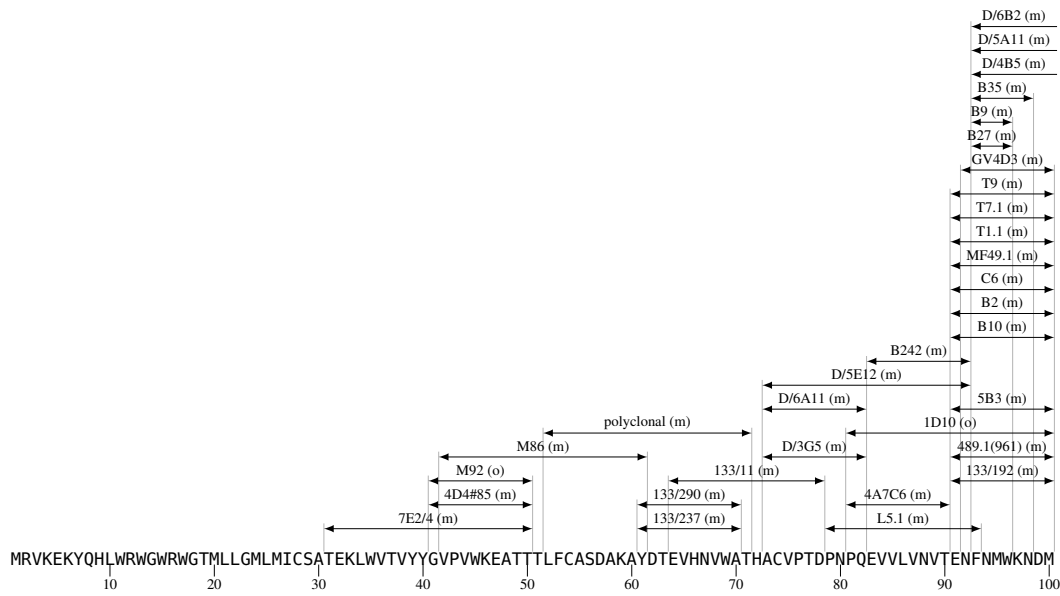
IV-D-11 Rev Ab Epitope Map



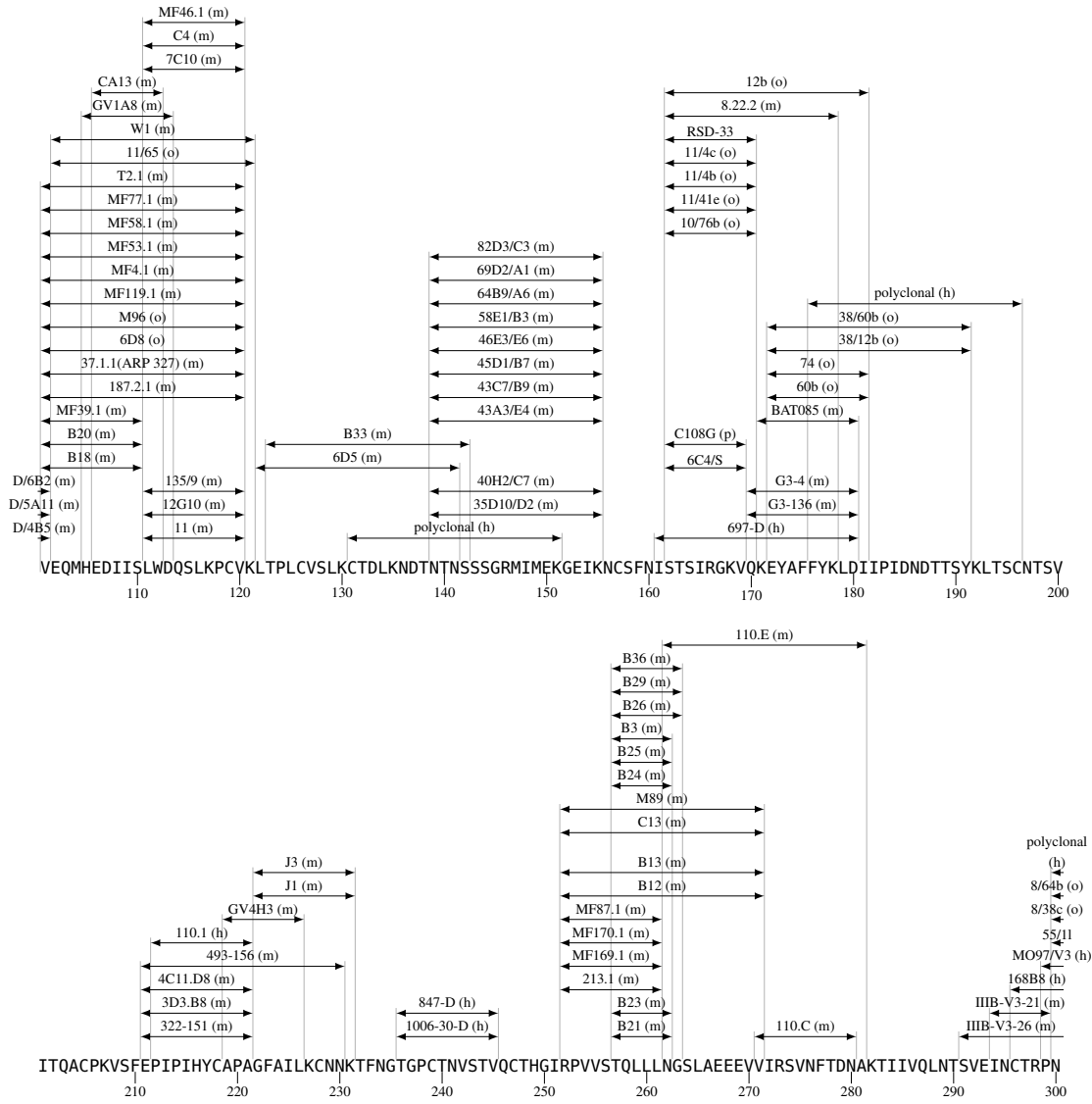
IV-D-12 Vpu Ab Epitope Map



IV-D-13 gp160 Ab Epitope Map

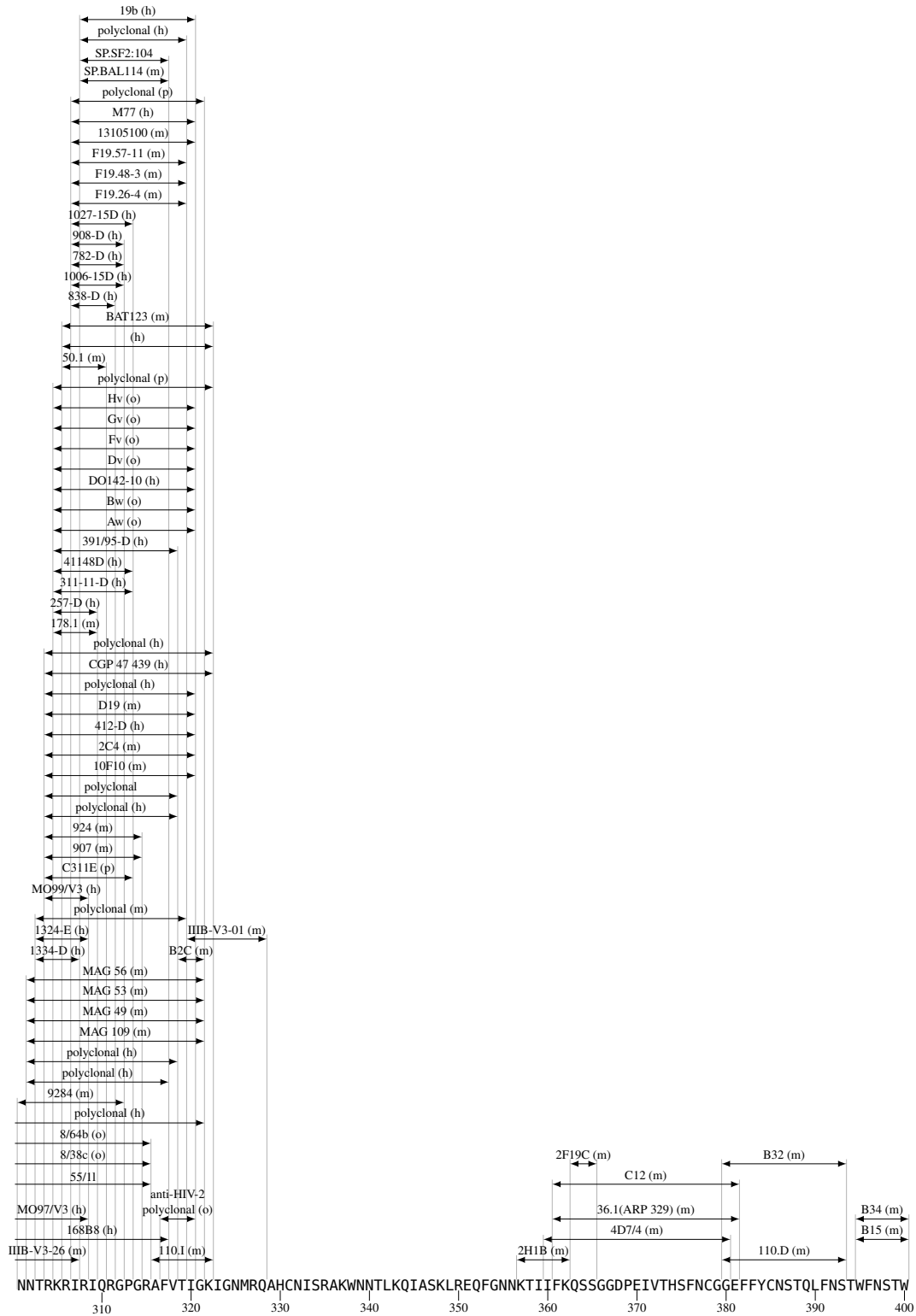


B Cell

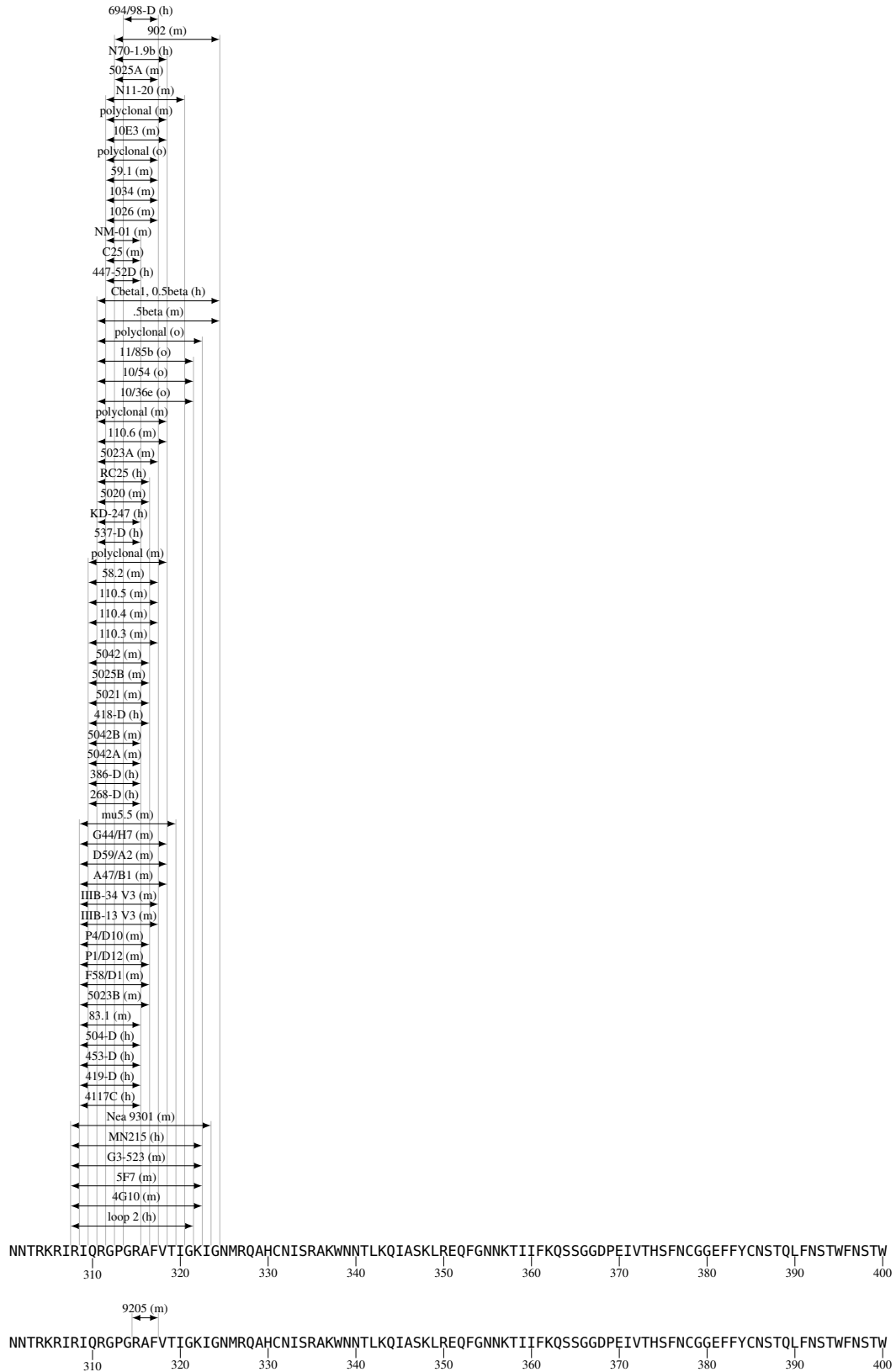


B Cell

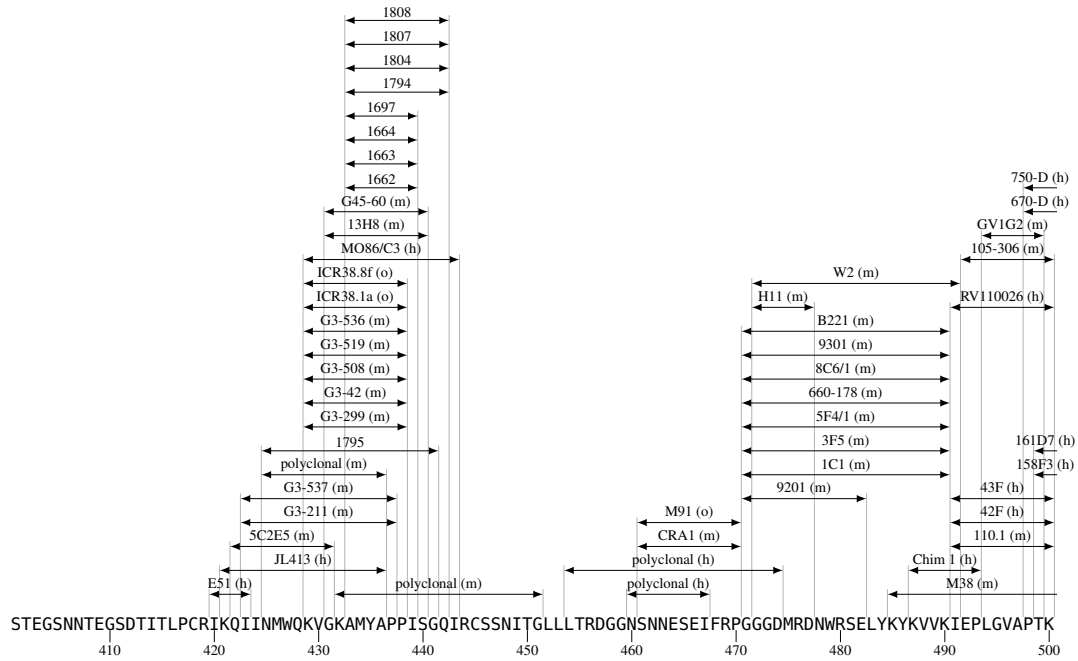




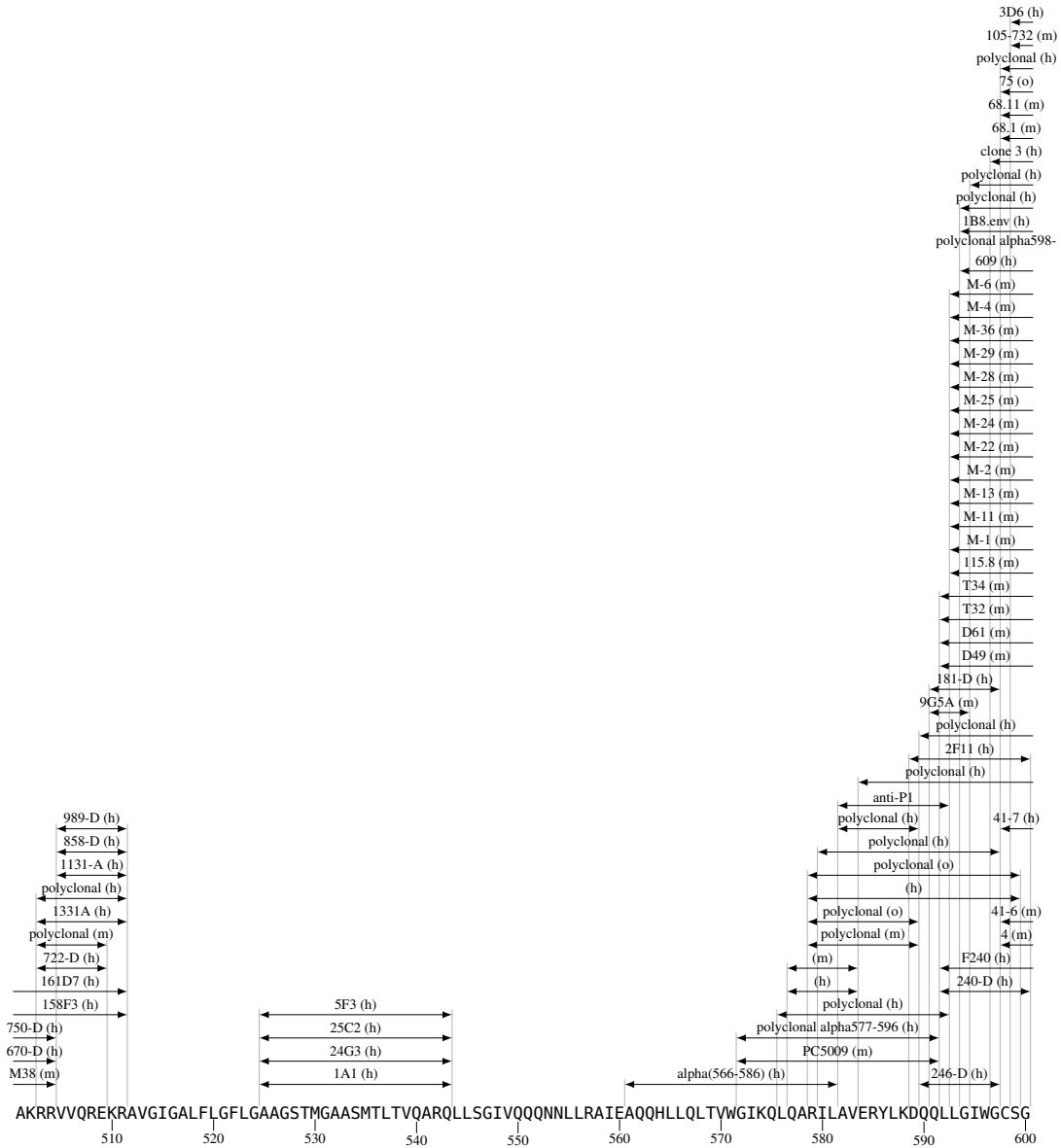
B Cell



B Cell



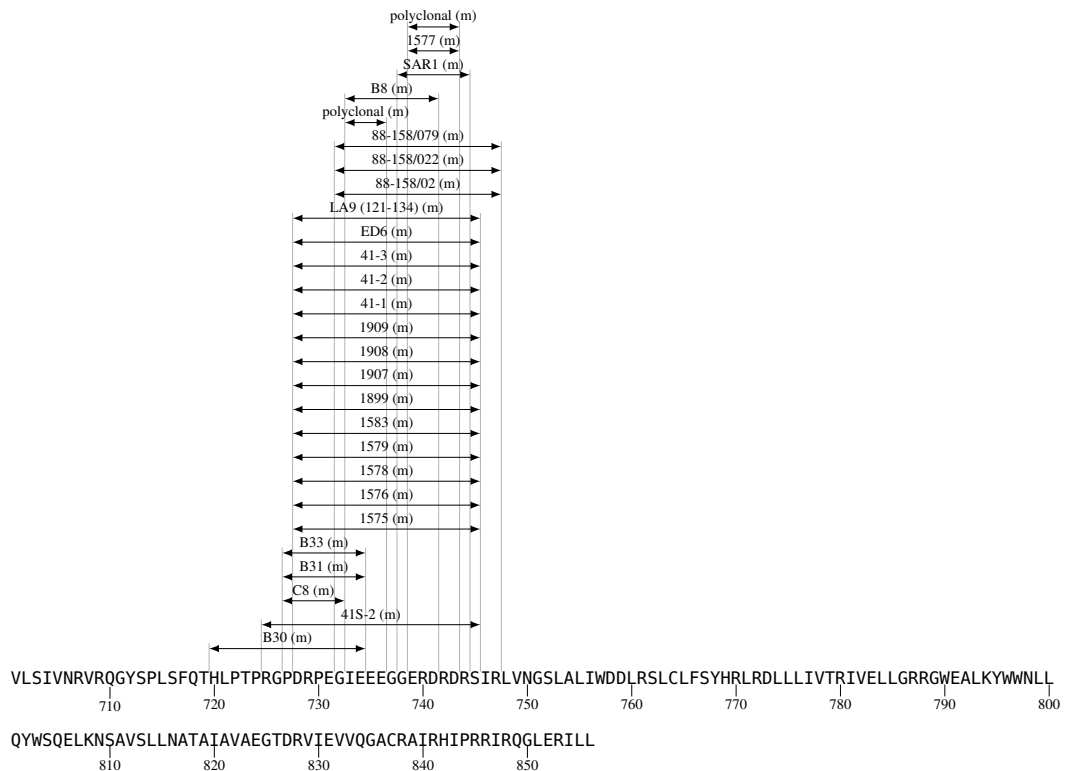
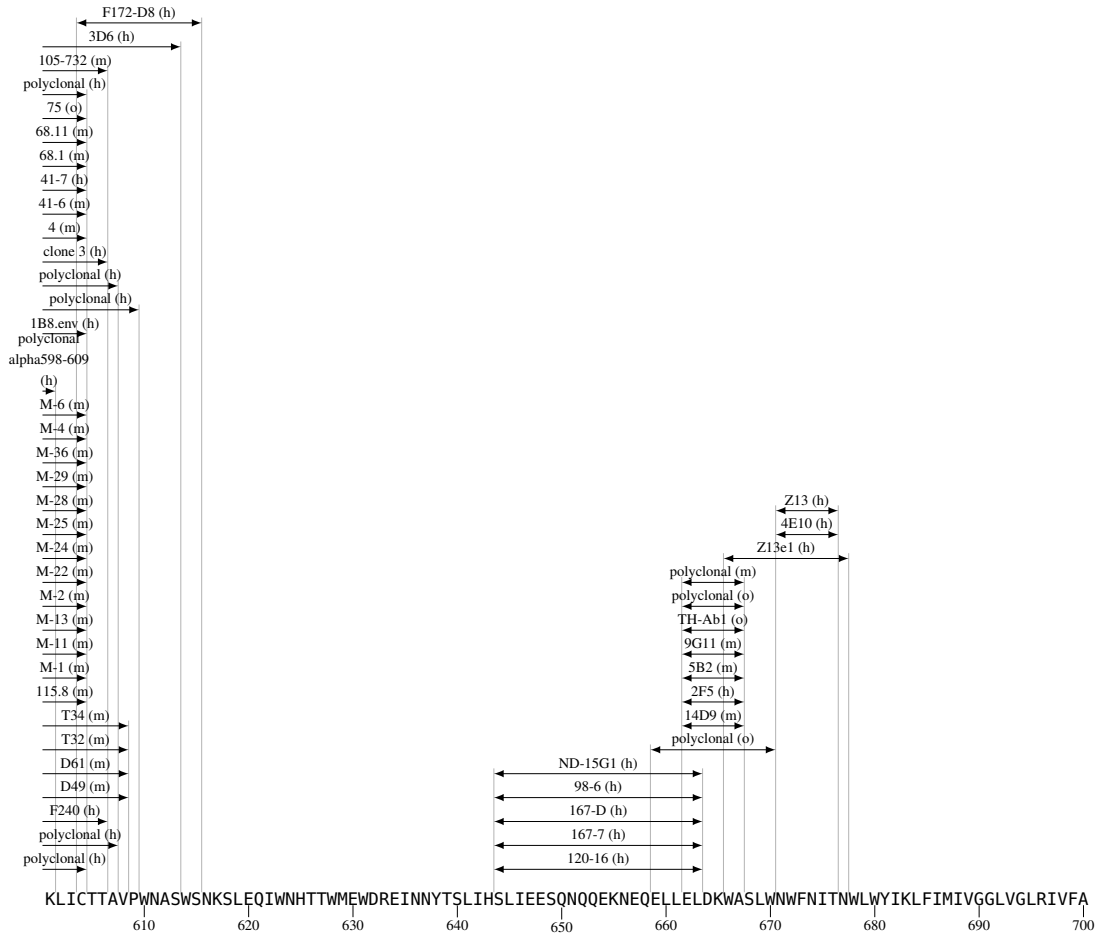
B Cell



B Cell

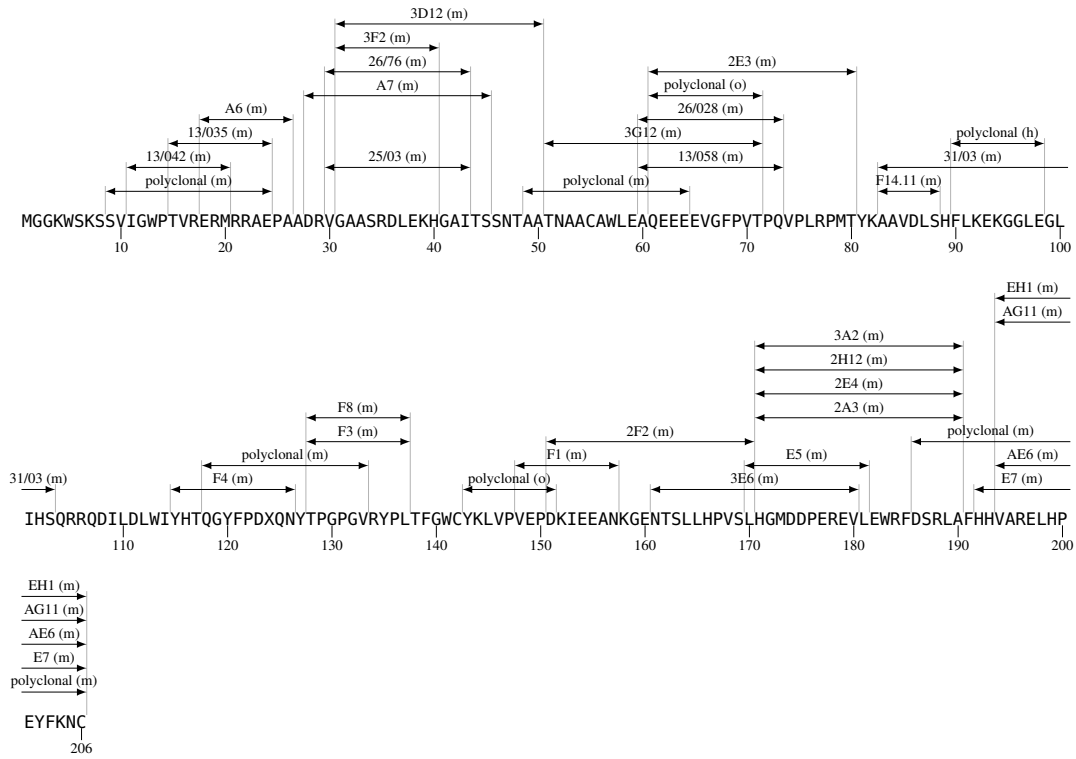
gp160 Ab Epitope Map

Maps of MAb Locations Plotted by Protein



B Cell

IV-D-14 Nef Ab Epitope Map



**Part V**

# **HIV Immunology References**





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## HIV Immunology References

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## HIV Immunology References

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## HIV Immunology References

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## HIV Immunology References

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